NDA 21-319; Supplement S-024
AVODART® (dutasteride) Soft Gelatin Capsule

GlaxoSmithKline

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Advisory Committee Briefing Document
Avodart for the Reduction of Risk of Prostate Cancer
Oncology Drugs Advisory Committee

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EXECUTIVE SUMMARY

Background

GlaxoSmithKline (GSK) submitted a Supplemental New Drug Application (sNDA 21-319) to the FDA in March 2010 to support the approval of dutasteride for the reduction of risk of prostate cancer in men at increased risk of developing the disease. Dutasteride is a competitive and specific inhibitor of both Type 1 and Type 2 5α-reductase that lowers serum dihydrotestosterone (DHT), the male hormone that leads to benign prostate growth as well as malignant growth. Dutasteride inhibits 5α-reductase isoenzymes in a dose-related fashion, with doses ≥ 0.5 mg daily reducing DHT in serum and prostate by ≥94%. Basic science research has shown that Type 1 5α-reductase is increased in prostate cancer and both 5α-reductase isoenzymes are elevated in high grade and advanced disease. Dutasteride has been available for treatment of benign prostatic hyperplasia (BPH) since 2003.

The principal evidence for the efficacy and safety of dutasteride for the proposed indication of reduction in the risk of prostate cancer in men at increased risk of developing the disease comes from the pivotal Phase III, 4-year Study ARI40006 (REDUCE) (Table 1). In addition to REDUCE, the Phase III Study ARI40005 (CombAT) supports the safety of dutasteride over 4 years in subjects with moderate to severe symptomatic benign prostatic hyperplasia. Data from ongoing Study ARI103094, which includes observational follow-up of subjects who had participated in REDUCE were also included in the sNDA. With agreement from the FDA, data from the recently completed Study AVO105948 (REDEEM), a 3-year study of dutasteride in subjects with localized low risk prostate cancer, was submitted to FDA after filing the sNDA and are included in this briefing document. This trial provides additional comparative information on cancer progression rates in dutasteride and placebo as well as frequency of tumor upgrading from low to high Gleason grade in both treatment groups.

Table 1 Studies Supporting the sNDA

Study ID	Description	N	Study Endpoints
ARI40006 (REDUCE) Phase III (Pivotal Study)	A randomised, double-blind, placebo-controlled, parallel group study of the efficacy and safety of dutasteride 0.5 mg administered orally once daily for 4 years to reduce the risk of biopsy-detectable prostate cancer.	8231 1:1 Randomization Dutasteride: 4105 Placebo: 4126	Primary: Biopsy-detectable PCa after 2 and 4 years of treatment Secondary: Gleason score at diagnosis, HGPIN at diagnosis, intervention for PCa, cancer characteristics (e.g., volume), etc.
ARI103094 Phase III Follow-up to ARI40006 Incomplete	Two year observational follow-up study for 4-year ARI40006 study subjects	2794 (4 Feb 2010)	PCa events, concomitant medication, PCa treatment, SAEs assessments
ARI40005 (CombAT) Phase III Supportive safety	A randomised, double-blind, parallel group study to investigate the efficacy and safety of treatment with dutasteride (0.5 mg) and tamsulosin (0.4 mg), administered once daily for 4 years, alone and in combination, on the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic benign prostatic hyperplasia	4844 1:1:1 Randomization Dutasteride: 1623 Tamsulosin: 1611 Combination: 1610	Primary: Time to first AUR or BPH-related surgery Secondary: AUR during study, BBH-related AUR during study, AUR on treatment, BPH-related surgery, health outcomes measures (IPSS)
AVO105948[a] (REDEEM) Phase IV Supportive efficacy and safety	A randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of dutasteride in extending the time to progression of low-risk, localized prostate cancer in men who are candidates for or undergoing expectant management	302 Dutasteride: 147 Placebo: 155	Primary: Time to PCa progression Secondary: Time to primary therapy for PCa, time to pathological progression, etc.

AUR: acute urinary retention; Combination = dutasteride plus tamsulosin; PCa = prostate cancer; SAE = serious adverse event

a. Study AVO105948 was not included in the sNDA for the indication of reduction of biopsy-detectable PCa.

Based on the pivotal Phase III REDUCE study population, the proposed indication is:

- "AVODART is indicated for reduction in the risk of prostate cancer in men at increased risk of developing the disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA)."

Medical Need

In the US prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer death in men [American Cancer Society, 2010]. New cases of prostate cancer and deaths due to prostate cancer in 2010 are projected as 217,730 and 32,050, respectively [National Cancer Institute, 2010]. The number of incident prostate

cancer cases is projected to grow steadily by almost 40% to more than 344,000 cases in 2025 due solely to increasing life expectancy and ageing of the population [Jemal, 2010].

Currently, prostate cancer diagnosis and management are associated with considerable human and economic burden. In 2006, the US spent 9.9 billion dollars on prostate cancer care, making it the fifth most costly cancer in the US that year [National Cancer Institute, 2010]. The process of prostate cancer screening and performance of diagnostic procedures can have a negative effect on mental well-being. Men may experience anxiety throughout the screening process, with the wait for biopsy results being a particularly stressful event [Dale, 2005]. Also biopsies can be painful and result in complications [Lee, 2006]. A positive diagnosis can lead to further distress of the patient [Korfage, 2006]. The diagnosis of prostate cancer can have a significant, negative effect on vitality, social, functioning, role emotional, mental status, and anxiety [Love, 2008].

Since 1 in 3 prostate biopsies result in a positive diagnosis of prostate cancer, [Welch, 2007] approximately 650,000 biopsies will be performed in the US in 2010. Most of the prostate cancers diagnosed will be low grade cancers that would unlikely cause morbidity if left untreated. In fact, approximately 65% of cancers detected have a Gleason score of ≤ 6 which is considered to be low-grade cancer. Of men diagnosed with prostate cancer, almost 90% will receive treatment regardless of the grade of their cancer [Andriole, 2009].

The most common treatments for newly diagnosed prostate cancer are radical surgery, external beam radiation therapy and brachytherapy. Frequently those treatments are associated with significant adverse events (AEs) including erectile dysfunction, urinary and bowel dysfunction. The impact of those AEs on quality of life should not be underestimated as men diagnosed with localized prostate cancer can live many years with the sequelae of these treatments [Albertsen, 1995].

Therapies to reduce the risk of developing prostate cancer would be an important addition to current management options for both patients and prescribers. AUA/ASCO guidelines have recommended that asymptomatic men with a PSA ≤3.0 ng/mL who are regularly screened with PSA or are planning to undergo annual PSA screening for early detection of prostate cancer may benefit from a discussion on the benefits and risks of 5ARIs for prostate cancer risk reduction [Kramer, 2009]. They also recognized that even if risk reduction of prostate cancer does not translate to a reduction of mortality, the impact on reducing the diagnosis and associated morbidities is a relevant endpoint.

The REDUCE trial for Reduction of Risk of Prostate Cancer

The pivotal study, ARI40006 (REDUCE) was a Phase III, international, multicenter, randomized, double-blind, placebo-controlled, parallel group study. It was designed to evaluate the efficacy and safety of oral, once daily dosing of 0.5 mg of dutasteride for 4 years in reducing the risk of biopsy-detectable prostate cancer in men considered to be at increased risk for prostate cancer. Subjects at increased risk for prostate cancer recruited into the study were males aged between 50 and 75 years with an elevated PSA value (≥2.5 ng/mL and ≤10 ng/mL for men aged ≥50 to ≤60 years, or ≥3.0 ng/mL and ≤10 ng/mL for men aged >60 to ≤75 years) and with a single negative prostate biopsy of

6 to 12 cores in the preceding 6 calendar months. Thus the study subjects were men of most concern to physicians, those with an elevated PSA, and a prior negative for-cause biopsy.

Eligible subjects completed a 4-week placebo run-in phase followed by randomization, by center, to either 0.5 mg dutasteride or matching placebo in a 1:1 ratio for a 4-year treatment phase. After the 48 month treatment phase, subjects entered a 4-month safety follow-up phase. The total study duration for each subject, including the one month placebo run-in phase was up to 53 months. The overall median exposures to study drug were similar in the placebo and dutasteride groups (1455 and 1456 days, respectively). Most subjects (≥85%) were treated with investigational product for at least 721 days (approximately 2 years) and ≥61% were treated for greater than 1440 days (4 years).

The primary efficacy endpoint was biopsy-detectable prostate cancer after 2 and 4 years of treatment.

Rationale for the REDUCE study design

The study required that subjects had a negative prostate biopsy prior to enrolling and 2 study-mandated biopsies at Year 2 and Year 4 of the study. The prior negative biopsy indicated that the physician had a clinical concern about prostate cancer. Also, the required entry biopsy excluded men with large aggressive tumors who might be least likely to benefit from dutasteride. The protocol-mandated biopsies at 2 and 4 years of treatment were an important part of the REDUCE study design. Because dutasteride causes decreases in PSA levels, and PSA change is the usual trigger for biopsies, the required biopsies ensured that all subjects were evaluated for the primary endpoint, having an equal chance of being diagnosed with cancer during the course of the study.

These protocol-mandated or scheduled biopsies insured that prostate cancer detection would be independent of PSA levels. If PSA-triggered biopsies were decreased by dutasteride, it might be expected that a lower number of subjects treated with dutasteride compared with subjects treated with placebo would be assessed or biopsied. For-cause biopsies, unscheduled and for clinical concern, were permitted, if clinically indicated. However, avoiding large numbers of for-cause biopsies driven by PSA, would allow us to determine if changes in PSA truly predict the likelihood of cancer. PSA levels were routinely doubled in reports to investigators so that they were blinded to subjects' treatment.

The classic *Gleason system* was used to grade the tumors of subjects in the REDUCE trial. Lower Gleason scores describe well-differentiated, less aggressive tumors. Higher scores describe less differentiated, more aggressive tumors (see Appendix C Section 12.3 for additional details). The classic Gleason scoring system is based solely on the architectural pattern of the tumor. A Gleason grade (pattern) of 1 to 5 is assigned to the 1st and 2nd most predominant patterns present in >5% of the tumor specimen and the grades are added together to obtain the Gleason score. The grade for the primary pattern is doubled if this pattern is present in ≥95% of the specimen. The presence of a 3rd pattern is not considered in the overall Gleason score calculation. From a practical perspective, Gleason grades 1 and 2 are rarely used to describe cancers in biopsy

specimens. Therefore, the lowest Gleason score commonly present on biopsies is Gleason 6 (3+3).

In 2005, The International Society of Urological Pathology (ISUP) modified the classic Gleason scoring (modified Gleason scoring) so that: The predominant pattern in the specimen is classified as the primary overall grade. The existence of any higher Gleason pattern, regardless of volume, is classified as the overall secondary grade, and added to the primary grade. Secondary patterns present in <5% of the total cancer are included in the modified scoring approach. Large cribriform glands are classified as Gleason pattern 4 (previously classified as Gleason pattern 3). Because of concerns that the classic Gleason scoring system might under-report the presence of high grade cancers (Gleason score 7-10), cancers detected during the REDUCE study were re-evaluated after the conclusion of the study using the modified Gleason scoring system.

Clinical Efficacy of Dutasteride for Reduction of Risk of Prostate Cancer

- REDUCE demonstrated that dutasteride treatment for up to 4 years reduced the relative risk of biopsy-detectable prostate cancer by 23.3% ($p<0.0001$) compared with placebo using the efficacy population and the crude rate approach, which includes all subjects at risk at the beginning of each time period (95% CI: 15.6%, 30.3%). More subjects in the placebo group than in the dutasteride group were diagnosed with prostate cancer during the study treatment phase (858/4073 subjects in the placebo group [21.1%] and 659/4049 subjects in the dutasteride group [16.3%]). There were approximately 200 fewer cancer cases among men taking dutasteride and their absolute risk reduction was 5%.

    - In both treatment groups, the incidence of prostate cancer was higher in Years 1-2 (14.2% of placebo subjects and 10.7% of dutasteride subjects) than in Years 3-4 (9.9% of placebo subjects and 7.9% of dutasteride subjects).

    - The relative risk reduction of prostate cancer did not vary significantly among sub-groups defined by age, family history of prostate cancer, baseline prostate specific antigen (PSA) level, time period and evaluation method.

Based on the data from REDUCE, 19 men (95% CI: 13.9, 30.4) at increased risk of developing prostate cancer would need to be treated with dutasteride for 4 years to prevent 1 diagnosis of prostate cancer.

Additional Risk Reductions in REDUCE

- Similar relative risk reductions for biopsy-detectable prostate cancer were observed when using pre-specified sensitivity analyses: the modified crude rate approach, which includes subjects who either were diagnosed with prostate cancer during the study or had and end of study biopsy (23.1%; 95% CI: 15.5%, 30.0%) and the restricted crude rate approach, which includes all subjects having at least one biopsy (22.8%; 95% CI: 15.2%, 29.8%).

- The relative risk for dutasteride subjects was consistent throughout the treatment period (0.76 in Years 1- 2, 0.79 in Years 3-4, and 0.77 overall, using the crude rate approach). The relative risk was similar with for-cause biopsies (0.74).
- Dutasteride reduced the number of for-cause biopsies compared with placebo (323 vs. 454, respectively), and among those positive for cancer, identified a higher proportion of high grade cancers (56% vs. 35%, respectively), and conversely, a lower proportion of low grade cancers (44% vs. 65%, respectively) were detected.

Dutasteride Effect on PSA/Low and High Grade Tumors

- The reduction in PSA by dutasteride did not interfere with the ability of using PSA levels to detect prostate cancer, including high grade tumors when the label recommendations for monitoring PSA increases from nadir are followed.
- Consistent with epidemiological data, the most prevalent cancers diagnosed were low grade cancers (Gleason score ≤6). Dutasteride significantly reduced low grade cancers compared with placebo (437/3299, 13.2% and 617/3407, 18.1%; p<0.0001). There was no overall increase in the percentage of high grade cancers (Gleason score 7-10) in the dutasteride group compared with the placebo group (220/3299, 6.7% vs. 233/3407, 6.8%).
- There was a numerical difference in the subset of Gleason score 8-10 cancers diagnosed throughout the four year period in the dutasteride group (29 subjects, 0.9%) compared with placebo (19 subjects, 0.6%) that did not reach statistical significance.
    - The difference in Gleason score 8-10 cancers between the dutasteride and placebo groups was most notable during Years 3-4, with only one such cancer diagnosed in the placebo group versus 12 in the dutasteride group. While the proportion of subjects in the dutasteride group with Gleason score 8-10 cancers remained constant over time (0.5% at Years 1-2 and Years 3-4), in the placebo group the proportion of cancer diagnosed dropped substantially from Years 1-2 (0.5%) to Years 3-4 (<0.1 %).
    - Rereads of the needle biopsy positive cancers by a second pathologist using principles of the modified Gleason scoring methodology, which simplifies the calculation of overall Gleason scoring, resulted in a high level of concordance (83%) between the original scoring used in the REDUCE study (classic Gleason score) and the rereads. The dutasteride treatment effect and patterns over time, in essence, did not change.

Multiple factors for the "difference" in Gleason 8-10 cancers during Years 3-4:

- Study design bias: compared to dutasteride, in the placebo group 141 more subjects were diagnosed with prostate cancer Gleason ≤7 at Years 1-2 and were withdrawn from study drug and subsequent biopsy at Years 3-4. This resulted in a nonrandomized distribution of cancer burden across treatment groups in Years 3-4 of the study. Should those excess 141 placebo-treated patients with cancers have remained in the trial and been rebiopsied at Years 3-4, some of their cancers would have been upgraded to a higher Gleason score (8-10). [e.g., Choo, 2007]

- Prostate volume bias: dutasteride reduced prostate volume which could have made cancers easier to detect
    - At the Year 2 biopsy the adjusted mean prostate volume decreased by 17.4% in the dutasteride group compared with a mean increase in the placebo group of 13%.
    - At the Year 4 biopsy, the adjusted mean prostate volume decreased by 17.5% in the dutasteride group, but increased in the placebo group by 19.7%, resulting in an adjusted mean difference between treatments in percentage change from baseline of -37.1% ($p<0.0001$). The adjusted mean prostate volumes of the dutasteride group were similar in Year 2 and Year 4 while the volumes in the placebo group continued to increase from Year 2 to Year 4.
- Increased accuracy in grading the biopsied tumors in the dutasteride group as observed in the grading during subsequent radical prostatectomies. Similar to what was reported with the 5ARI finasteride [Lucia, 2007], 58.6% of cancers of subjects in the dutasteride group who underwent prostatectomies after biopsy were accurately graded compared with 50% of those in the placebo group. Dutasteride-induced preferential suppression of the low grade component of prostate cancers could have increased the likelihood that the remaining cancers would be diagnosed as high grade tumors [Lucia, 2007].
- Dutasteride could have induced high grade cancers. The preponderance of data from basic science findings do not support a dutasteride-induced increase in high grade cancers over time and no similar observation has been made in other randomized dutasteride trials such as REDEEM, and CombAT. No increase in high grade tumor over time was observed with finasteride in a 7 year randomized-control risk reduction trial in a low risk population [Thompson, 2003].

Although a causal relationship between dutasteride therapy and Gleason score 8-10 cancers has not been established, an additional Warnings and Precaution with a description of the high grade tumor findings in REDUCE, as well as detailed information on patient monitoring and the significance of increases in PSA relative to high grade cancers diagnosis has been added to the dutasteride labeling. Dutasteride does not interfere with the detection of high grade tumors using PSA if the recommendations in the label are followed.

Other benefits of dutasteride for this patient population include:

- Significant reduction in the relative risk of the prostate cancer precursor lesion, High Grade Prostatic Intraepithelial Neoplasia (HGPIN), of 43.3% (4% vs. 7%, respectively, $p<0.0001$) compared with placebo. Significant reduction in the relative risk of the prostate cancer associated lesion, Atypical Small Acinar Proliferation (ASAP) of 23.5% (3% vs. 4%, respectively, $p=0.0205$).compared with placebo.
- Fewer post-biopsy adverse events including hematuria, hematospermia and UTI (total post-biopsy events: 4.4% vs. 7.3% for dutasteride vs. placebo, respectively, $p<0.0001$).

- Fewer interventions, both surgical and non-surgical, for treatment of prostate cancer (7.4% vs. 10.8% for dutasteride vs. placebo respectively, $p<0.0001$).
- The number of total cumulative days (TCD) of hospitalization for prostate cancer surgeries and prostate-related surgeries was lower in the dutasteride group than in the placebo group. In general, TCD of hospitalization for prostate-related interventions and events, was also lower in the dutasteride group compared with the placebo group, with the exception of hospitalization due to drug therapy, external beam radiation, and macroscopic hematuria where the number of subjects was low (1 to 7 subjects per treatment group).

Beneficial effects on BPH symptoms and related events:

- Significant reduction in BPH symptoms measured by the International Prostate Symptom score (IPSS) questionnaire in the dutasteride group vs. increase in the placebo group. Placebo subjects showed deterioration while dutasteride subjects showed improvement in their BPH symptoms.
- Improved patient-reported outcomes and BPH-related quality of life including measures from the BPH Impact Index and NIH Chronic Prostatitis Symptom Score.
- Alpha blocker use for BPH management was initiated by 18.9% placebo vs. 12.7% dutasteride subjects, $p<0.0001$.
- Significant reduction in the relative risk of acute urinary retention (AUR) by 77%, 6.7% placebo vs. 1.6% dutasteride, $p<0.0001$.
- Significant reduction in the relative risk of urinary tract infections (UTI) by 41%, 8.8% placebo vs. 5.3% dutasteride, $p<0.0001$.
- Significant reduction in the relative risk of BPH- related surgery by 73%, 5.1% placebo vs. 1.4% dutasteride, $p<0.0001$.

Prostate Cancer Findings in Other Randomized Dutasteride trials:

- **REDEEM**: In this 3-year localized low risk prostate cancer trial, there was no difference in high grade tumors in subjects treated with dutasteride vs. placebo (Gleason score 7: 17 subjects vs. 19 subjects, respectively; Gleason score 8: 2 subjects vs. 3 subjects, respectively) at the Year 3 biopsy. There were no Gleason score 9 and 10 cancers reported in either treatment group. There was a decrease in Gleason score 6 cancers in subjects treated with dutasteride vs. placebo at Year 3 biopsy (71 vs. 83 subjects, respectively) and an increase in the number of men with no cancer detected on their final biopsy, 50 vs. 31 subjects, respectively.
- **CombAT:** In this 4-year BPH trial, there was an overall 40% reduction in prostate cancers in the dutasteride treatment groups, and a numerical reduction in all categories of Gleason score prostate cancers (≤ 6, 7, and 8-10), reported as an adverse event (AE) in the dutasteride treatment groups of the study compared to tamsulosin monotherapy group. The numbers of biopsies were decreased in the dutasteride arms; if a subject was biopsied, the results were more likely to be positive

for cancer in the two dutasteride groups than the tamsulosin monotherapy group (28-29% vs. 24%).

- Phase III randomized BPH trials: A reduction of 51% in prostate cancer diagnoses were reported for dutasteride treated subjects compared with placebo subjects [Andriole, 2004].

Clinical Safety of Dutasteride

- In the REDUCE trial, there were no significant differences between the dutasteride and placebo groups in the percentages of subjects with any AE, any SAE, or fatal SAEs (Table 2). The incidences of drug-related AEs and AEs leading to withdrawal were higher in the dutasteride group. The most common drug-related AEs were those related to sexual function, with no more than 4% increase in the dutasteride group compared with placebo. These events were reported primarily during the first 6 months of treatment, were mainly mild to moderate in severity, rarely led to drug withdrawal, and would occasionally resolve while on therapy. Similar results were seen in the CombAT trial. The observed safety profile for dutasteride in the REDEEM study population was consistent with the profile in other studies of dutasteride.

Table 2 Number (%) of Subjects with Most Common AEs, Drug-Related AEs, SAEs (Fatal and Non-fatal), AEs leading to Permanent Discontinuation of Study Drug and AEs leading to Withdrawal from Study (REDUCE Safety Population)

AE Type Preferred Term	Placebo N=4126 n (%)	Dutasteride N= 4105 n (%)
Any AE	2966 (72)	3017 (73)
Erectile dysfunction	363 (9)	494 (12)
Hypertension	330 (8)	355 (9)
Nasopharyngitis	288 (7)	313 (8)
Back pain	247 (6)	265 (6)
Influenza	213 (5)	204 (5)
Any drug-related AE	604 (15)	904 (22)
Erectile dysfunction	237 (6)	369 (9)
Libido decreased	65 (2)	137 (3)
Loss of libido	54 (1)	79 (2)
Gynaecomastia	43 (1)	76 (2)
Semen volume decreased	9 (<1)	56 (1)
Any SAE	837 (20)	748 (18)
Fatal SAEs[a]	74 (2)	70 (2)
Non-fatal SAE	784 (19)	699 (17)
Any AE leading to study drug discontinuation	244 (6)	342 (8)
Erectile dysfunction[b]	28 (<1)	66 (2)
Any AE leading to withdrawal from study	284 (7)	388 (9)
Erectile dysfunction[b]	28 (<1)	72 (2)

a. All AEs in this category were reported by <1% of subjects in each treatment group.
b. All other AEs in this category were reported by <1% of subjects in each treatment group.

- The safety profile of dutasteride in the REDUCE and CombAT trials were generally consistent with previous BPH studies and 7 years post-marketing experience with the exception of the difference in Gleason 8-10 cancers as noted above and in cardiac failure events in REDUCE (dutasteride, 0.7% and placebo, 0.4%) and in CombAT (dutasteride + tamsulosin combination therapy group, 0.9%,. dutasteride monotherapy group, 0.2% and tamsulosin monotherapy group 0.6%,). There were no differences between treatment groups in overall cardiovascular events, events consistent with congestive heart failure, major adverse cardiovascular events (MACE), or cardiovascular deaths. Considering all data from the >10,000 men exposed to dutasteride in clinical trials as well as post-marketing experience, no causal relationship between use of dutasteride and cardiac failure has been established. These data have been extensively reviewed and FDA has adjudicated the cases. With FDA input, the cardiac failure results of REDUCE and CombAT have been added to the product labeling under "Adverse Reactions".
- No clinically relevant trends were noted for other safety data including laboratory parameters, vital signs, gynecomastica evaluations or digital rectal examinations.

Benefit: Risk

Given the totality of the data, the benefit: risk profile of dutasteride for reducing the risk of prostate cancer in men who are at increased risk of developing the disease is favorable. Significant reductions were found for the risk of prostate cancers overall, the proportion of subjects with the most prevalent cancer type (Gleason score ≤6), prostate cancer precursor and associated lesions (HGPIN and ASAP), post-biopsy adverse events, interventions for prostate cancer, and hospitalizations. Significant reductions were seen in the risk of BPH outcomes (AUR, BPH related surgeries and UTI events) as well as beneficial effects in BPH symptoms, patient reported outcomes and measures of QOL.

The safety profile is consistent with the findings from other clinical studies as well as post-marketing experiences with dutasteride, with 2 exceptions, cardiac failure and Gleason 8-10 tumors. Although a causal relationship between dutasteride and these events has not been established, the proposed label includes updated wording in the "Adverse Reactions" section informing about cardiac failure and high grade tumor study findings, as well as detailed information in the "Warnings and Precaution" section on patient monitoring and the significance of increases in PSA relative to high grade cancer diagnosis for adequate patient management.

There is no currently approved therapy for prostate cancer risk reduction. Dutasteride could provide an option to patients at risk to reduce their chances of being diagnosed and subsequently treated for this highly prevalent disease.

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Abbreviations

ACE	Angiotensin converting enzyme
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ALP	Alkaline phosphatase
AST (SGOT)	Aspartate aminotransferase
AUC	Area Under the Curve
AUR	Acute Urinary Retention
5ARI	5 Alpha Reductase Inhibitor
ASAP	Atypical Small Acinar Proliferation
BII	BPH Impact Index
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
CaPSURE	Cancer of the Prostate Strategic Urological Research Endeavor
CI	Confidence Interval
CombAT	Combination of Avodart and Tamsulosin
CRF	Case Report Form
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
DRE	Digital Rectal Examination
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
GSK	GlaxoSmithKline
HGT	High grade tumor
HGPIN	High Grade Prostatic Intraepithelial Neoplasia
HRQOL	Health-related Quality of Life
IPSS	International Prostate Symptom score
ISUP	International Society of Urological Pathology
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiac Events
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MOS Sleep-6	Medical Outcomes Study Sleep-6 Sleep Scale
NIH CPSI	National Institutes of Health Chronic Prostatitis Symptom Index
NPV	Negative Predictive Value
NSAID	Non-Steroidal Anti-Inflammatory Drug
OC	Observed Cases
PAS SFI	Problem Assessment Scale of the Sexual Function Index
PCa	Prostate cancer
PCPT	Prostate Cancer Prevention Trial
PIN	Prostatic Intraepithelial Neoplasia
PSA	Prostate Specific Antigen
PPV	Positive Predictive Value
PV	Prostate Volume
PVRV	Post Void Residual Volume
Qmax	Maximum (peak) flow rate

QOL Q8	Quality of Life Due to Urinary Symptoms
REDUCE	REduction by DUtasteride of Cancer Events
REDEEM	REduction by Dutasteride of clinical progression Events in Expectant Management
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SEER	Surveillance Epidemiology and End Results
T	Testosterone
TCD	Total cumulative days
TRUS	Transrectal ultrasound
UK	United Kingdom
US	United States
UTI	Urinary Tract Infection
WBC	White Blood Cells

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
AVODART	None

1. INTRODUCTION AND BACKGROUND

As an aging-related disease, the incidence of prostate cancer is expected to increase with increasing life expectancy. Currently, prostate cancer diagnosis and management is associated with considerable human and economic burden. Therapies to reduce the risk of developing prostate cancer as well as increase the detection of those cancers that are more likely to be associated with poorer outcomes, would be an important addition to current management options for both patients and prescribers.

1.1. Prostate Cancer: Nature of the Disease

Prostate cancer, unlike other solid tumors, varies in its biological behaviour. Prostate cancer is a multifocal and heterogenous disease with the potential of different cancers of varying aggressiveness existing in a prostate at the same time. These cancers vary in their growth and progression patterns and the challenge is to distinguish between the more common, latent, histological or clinically less aggressive form (low grade tumor) and the more aggressive form (high grade tumor) that is associated with poorer outcomes and death.

Most prostate cancers are slow growing and are confined to the prostate for many years. These cancers are referred to as low grade cancers according to the Gleason grading system (Appendix C, Section 12.3). During this latent phase, the prostate cancer produces no or few symptoms. As the cancer progresses, it can spread beyond the prostate and metastasize to other organs. Symptoms of prostate cancer are more often associated with advanced disease and include urinary and sexual dysfunction and pain, symptoms that are also associated with other diseases of the prostate (i.e. benign prostatic hyperplasia [BPH] and prostatitis). The aggressive forms of prostate cancer (HGT) are associated with poorer outcomes and death. Today, the majority of prostate cancers are diagnosed in men older than 65 years [American Cancer Society, 2009]. Due to the relatively advanced age at diagnosis, the current life expectancy, and the natural history of prostate cancer in which the majority of prostate cancers are the relatively low grade forms, most men with prostate cancer today will die from causes other than prostate cancer.

Therefore, for the majority of men at increased risk of prostate cancer, the most frequent harm derived from the disease is the morbidity and complications arising from its diagnosis, including unnecessary biopsies, inaccurate grading of biopsies and the adverse sequelae of subsequent treatments. Consequently, it is important to reduce the number of low grade cancers that start the whole and costly cascade of current prostate cancer management.

1.1.1. Epidemiology

In the United States (US), prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer death in men [American Cancer Society, 2010]. In

the US population 217,730 new cases of prostate cancer are expected to be diagnosed and a projected 32,050 men will die of prostate cancer in 2010 [National Cancer Institute, 2010]. The number of incident prostate cancer cases is projected to grow steadily to over 344,000 cases in 2025 due solely to increasing life expectancy and ageing of the population. As with total prostate cancer, the number of incident high grade Gleason score 8-10 prostate cancer is expected to rise from approximately 34,000 cases in 2010 to over 50,000 in 2025.

The introduction of Prostate Specific Antigen (PSA) testing in 1986 led to a large increase in the incidence of prostate cancer, as well as a shift in the type of prostate cancer detected with more low grade and organ-confined cases and lower mortality in those countries where PSA screening is widespread [Parkin2005; Jemal, 2008; Ferlay, 2007]. In contrast, PSA screening has had minimal impact on the incidence of high grade tumors (Gleason score 8-10). Over the past few decades in the US, the percentages of incident Gleason score 8-10 tumors among total incident prostate cancer for all races were 19 to 23% during the 1980's and generally under 20% thereafter. This trend is expected to continue such that the largest proportion of prostate cancer will be low grade cancers [SEER, 1973-2007]. The 10-yr prostate cancer-specific survival is nearly 100% for patients with Gleason score 2-6 tumors, and much higher than those with Gleason score 8-10 tumors (73%), regardless of treatment [SEER, 1973-2007].

1.1.1.1. Risk Factors

Established risk factors for prostate cancer include age, race and family history of prostate cancer. These risk factors apply to both low and high-grade prostate cancers. Although results from the Health Professional Follow-up Study (HPFS) suggest that the strength of these factors may vary for high-grade disease compared with low grade diseases [Giovannucci, 2007], data specifically comparing risk factors for high grade vs. low grade tumors are sparse. Other potential risk factors for prostate cancer include dietary, environmental and hormonal factors.

In clinical practice, the three established risk factors of age, race, and family history are usually considered in combination with serum PSA elevation and/or positive digital rectal examination (DRE) to trigger a prostate biopsy to assess the existence of cancer. A systematic review showed that, in general, total PSA, age, a positive family history, African-American ethnicity and/or a positive DRE significantly increase the chance of finding prostate cancer, whereas a larger prostate volume and a previous negative biopsy decrease the chance [Schröder, 2008].

1.2. Current Therapies and Unmet Medical Need

Given the difference between the incidence of prostate cancer and prostate cancer-related death, there is potential for over-detection and over-treatment of low aggressive cancers. Since 1 in 3 prostate biopsies result in a positive diagnosis of prostate cancer, approximately 650,000 biopsies will be performed in the US in 2010 [Welch, 2007]. Of these approximately 65% will be low grade cancers (Gleason score ≤6). Recent analyses of the US CaPSURE database showed that during the period 2004-2006, 90% of the low risk cancers (PSA <10 ng/mL, biopsy Gleason score of ≤6 and a clinical stage of T2a or

less) were treated. Almost 60% of the treatments were radical prostatectomies [Cooperberg, 2007].

In the US, the reduction in risk of prostate cancer is an important medical target for the patient, physician and society because of its high prevalence, associated morbidity and mortality, the morbidity associated with biopsies and treatment, its long latency period and the challenges of differentiating between aggressive (potentially lethal) high grade cancers and low grade, less aggressive disease.

To fully understand the potential clinical benefits of a risk reduction strategy for Prostate cancer, one needs to understand the limitations of current screening practices (Section 1.2.1) and the impact of diagnosis and treatment on both the patient and their family (Section 1.2.2).

1.2.1. PSA-Screening

The aim of any cancer screening program is to accurately detect the cancer at the earliest possible stage to optimize the chance of a cure, while at the same time minimizing diagnosis and treatment of cancers that are unlikely to cause harm if left untreated. PSA is the most important marker for detecting prostate cancer [Schröder, 2009a]. However, there is no single PSA cut-off level that provides optimal sensitivity and specificity in prostate cancer detection [American Urological Association, 2009], and the significance of any given PSA value changes with factors such as age and prostate volume. One of the challenges in today's practice is how to identify clinically meaningful changes in PSA that firstly justify a biopsy being performed and secondly are likely to be associated with clinically aggressive cancers.

1.2.2. Diagnosis and Treatment

Despite high survival rates, there is still considerable morbidity from both diagnostic biopsies (urinary tract infections, sepsis, and bleeding) and disease treatment (mainly sexual, urinary and bowel dysfunction) of prostate cancer.

The standard method of diagnosis is a prostate biopsy; however, this technique is currently associated with limitations in terms of performance and accuracy. It is estimated that up to one in four cancers could be missed at first biopsy [Tan, 2008; Welch, 2007; Djavan, 2001] and up to 27% of the Gleason scores assigned would be upgraded/ reclassified if a subsequent biopsy was performed [Berglund, 2008; Choo, 2007, Carter, 2002]. Complications associated with prostate biopsies are presented in Table 3. Significant bleeding and/or infection occur in 1 to 4% of patients who undergo biopsy [Ragavan, 2005]. A significant rise in hospital admissions for urological complications within 30 days of a prostate biopsy has been recently reported with the majority of admissions (72%) for infection-related reasons. Among subjects who were not diagnosed with prostate cancer (41,682/75,190, 55%) by the biopsy, the probability of being admitted to the hospital within 30 days of having a prostate biopsy increased 4-fold between 1996 and 2005 (OR 3.7, 95% CI 2.0 –7.0, $p<0.0001$). The overall 30-day mortality rate was 0.09% (64/75190 subjects), but did not change during the study period [Nam, 2010].

Table 3 Frequency of Biopsy Complications

Complications[a]	% of biopsies
Hemaetospermia	37.4
Hematuria (>1 day)	14.5
Rectal bleeding (<2 days)	2.2
Prostatitis	1.0
Fever	0.8
Epididymitis	0.7
Rectal bleeding (>2 days ± requiring surgical intervention)	0.7
Urine retention	0.2
Other complications requiring hospitalization	0.3

[National Comprehensive Cancer Network, 2010]

a. Complications from 10 core biopsy

The process of prostate cancer screening and performance of diagnostic procedures can have a negative effect on mental well-being. Men may experience anxiety throughout the screening process, with the wait for biopsy results being a particularly stressful event [Dale, 2005]. A positive diagnosis can lead to further distress of the patient [Korfage, 2006]. The diagnosis of prostate cancer can have a significant, negative effect on vitality, social, functioning, role emotional, and mental status, as measured by the SF-36 [Love, 2008]. Additionally, men diagnosed with prostate cancer have a greater rate of anxiety compared with aged-matched controls of men in the general population [Love, 2008].

Of the men diagnosed with prostate cancer, almost 90% will receive treatment (radical prostatectomy and radiation therapy for localized prostate cancer, with hormonal therapy and chemotherapy used in advanced stages of the disease) regardless of Gleason score [Andriole, 2009]. Other common management options for localized prostate cancer include active surveillance (watchful waiting, expectant management). If a patient chooses active treatment of prostate cancer, then the adverse consequences of active treatment can be significant, affecting almost every patient at some point during therapy. These adverse events affect the patient's health-related quality of life (HRQOL), in addition to burdening the healthcare system in terms of management costs and reduced patient function. Both radical prostatectomy and radiation therapy can cure localized prostate cancer; however, many are associated with significant increased risk of side-effects including sexual, urinary and bowel dysfunction compared to conservative treatment (Table 4) [Bhatnager, 2006].

Table 4 Risk of Erectile, Urinary and Bowel Symptoms Resulting from Prostate Cancer Treatment

ADVERSE EVENT	Number of Randomized Studies	Risk after Radical Prostatectomy (%)	Risk after External Beam Radiation (%)	Risk after Conformal Beam Radiation (%)	Risk after Brachytherapy (%)
Erectile Dysfunction	2	35[a]	47[b]	52[b]	--[c]
Urinary Symptoms	5				--[d]
Mild		30[a]	20-59	33-53	
Moderate to Severe			2-20	9	
Bowel Symptoms	3				
Mild			47-57	27-47	
Moderate to Severe			12	26	8

Source: [Bhatnager, 2006]

a. Excess risk after radical prostatectomy (risk after radical prostatectomy - risk under conservative management)
b. The incidence of erectile dysfunction increased from 15% at baseline to 47% among patients randomized to external beam radiation, and from 24% at baseline to 52% among patients randomised to conformal beam radiation
c. No randomised trials reported; rates of 8% in population-based studies and up to 50% in tertiary care institutions
d. No randomised trials reported; rates of up to 24% reported in tertiary care institutions

The impact of secondary side-effects of treatment on quality of life should not be underestimated as men diagnosed with localized prostate cancer can live many years with the sequelae of these treatments [Albertsen, 1995]. In men with aggressive prostate cancer, complications associated with treatment are most often considered acceptable if the treatment prolongs life or reduces morbidity from the disease. In men who harbor low grade and less aggressive disease, however, the common morbidities associated with treatment negatively impact quality of life and should be considered a potential harm associated with PSA screening [Penson, 2003].

Quality of life scales measuring anxiety, depression, sexual functioning, urinary functioning, urinary incontinence, urinary irritation or obstruction, bowel functioning, emotional and mental status have found these to be negatively affected by the prostate cancer-related treatments noted in Table 4, as well as by active surveillance and watchful waiting [e.g., Bellizzi, 2008; Burnett, 2007; Roeloffzen, 2009; Roobol, 2009; Sanda, 2008].

The patient's partner and family may also experience stress related to prostate cancer diagnosis, treatment-related worries and concern about physical limitation [Katz, 2007; Harden, 2005; Northouse, 2007].

In the end, for an optimal management decision, one has to balance the frequent treatment-related morbidities associated with prostate cancer treatment with the associated benefits of potentially curative treatments taking into consideration the patient's life expectancy, comorbid conditions, and general well-being.

1.2.3. Economic Impact of Prostate Cancer

In 2006, the US spent 9.9 billion dollars on prostate cancer care, making it the fifth most costly cancer in the US that year behind breast (13.9 billion), colorectal (12.2 billion), lung (10.3 billion), and lymphoma (10.2 billion)[National Cancer Institute, 2010] . The average cost of treating a patient with prostate cancer in the first year following diagnosis ranges from $21,040-$25,041 [Roehrborn, 2009; Crawford, 2010]. There are increasing numbers of patients diagnosed with prostate cancer and an increase in the proportion of elderly patients requiring treatment [Warren, 2008]. This imposes a substantial economic burden on healthcare providers and society – an economic burden which is only likely to increase as the number diagnosed with prostate cancer increases as the population ages.

1.2.4. Risk Reduction Therapies

Many types of drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], statins, vitamins, and dietary supplements) have been proposed to reduce the risk of prostate cancer, however, the evidence is inconclusive and none have been approved by the European Medicines Agency (EMA) or the Food and Drug Administration (FDA).

Diet has been considered for prevention of many cancers including prostate cancer; however, recent results of large studies of vitamin C, vitamin E and selenium have failed to demonstrate a benefit [Lippman, 2009; Gaziano, 2009; Peters, 2008]. Some epidemiological studies have suggested that statins and NSAIDs may reduce prostate cancer risk, but these findings have not been demonstrated in an appropriately powered and prospective randomized controlled study [Hamilton, 2008; Jacobs, 2007; Singer, 2008].

Over recent years, some of the most promising risk reduction data to emerge were for finasteride, a selective inhibitor of Type 2 5α-reductase, which is approved for the treatment of BPH and male pattern baldness. In the Prostate Cancer Prevention Trial (PCPT), finasteride reduced the overall risk of biopsy-detectable prostate cancer by about 25% compared with placebo (18.4% versus 24.4%) in men at low risk of prostate cancer [Thompson, 2003]. The clinical impact of these data was limited, as the study also showed an apparent 25% increased incidence of high grade tumors, defined as Gleason score 7-10 in the finasteride group compared with placebo (6.4% versus 5.1%). However, post hoc analyses indicate the difference was likely due to ascertainment bias.

The American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA) published joint guidelines for the use of finasteride and dutasteride for prostate cancer risk reduction [Kramer, 2009]. They recommend that men with a PSA ≤3.0 ng/mL who are regularly screened for PSA, and men who are taking or planning to take 5α-reductase inhibitors (5ARIs) for BPH symptoms, may benefit from a discussion with their physician of the benefits and risks of 5ARIs for the prevention of prostate cancer. These discussions would include the facts that there is no guarantee of preventing prostate cancer completely, there may be reversible sexual function side effects, and there is a possibility of developing high grade cancers.

These guidelines were based on a Cochrane Review [Wilt, 2008] that relied primarily on the PCPT trial in men with a baseline PSA of <3.0 ng/mL, who were not pre-selected for risk of developing prostate cancer. The Cochrane Review predated completion of REDUCE, the pivotal trial for the dutasteride sNDA that is detailed in this Briefing Document.

Current management practices would further benefit from approaches that:

- reduce the development of prostate cancer in men, particularly those at increased risk of developing the disease
- reduce the number of men referred for biopsy and subsequently unnecessarily diagnosed and treated for low grade prostate cancer without interfering with the diagnosis and treatment of high grade cancers
- reduce the burden on the patient, family members and the health systems.

1.3. Rationale for Dutasteride in Prostate Cancer Risk Reduction

The rationale for the development of dutasteride for prostate cancer risk reduction derives from the following:

- Dutasteride is a competitive and specific inhibitor of both Type 1 and Type 2 5α-reductase and it lowers serum Dihydrotestosterone (DHT), the main intraprostatic androgen related to normal and hyperplastic growth, in a dose-related fashion, with doses ≥ 0.5 mg daily reducing DHT in serum and prostate by ≥94%.

- Type 1 5α-reductase is elevated in prostate cancer and both 5α-reductase isoenzymes are elevated in high grade and advanced disease.

- In a pooled analysis of dutasteride Phase III BPH studies (N=4325 subjects), the cumulative incidence of prostate cancer, reported as an adverse event, was 51% lower over 27 months with dutasteride compared with placebo (27 subjects or 1.2% dutasteride versus 55 subjects or 2.5% placebo, p=0.002) [Andriole, 2004]. Although prostate cancer was not a prespecified endpoint in these studies and biopsies were only done as a for-cause biopsy, no prostate cancer risk reduction has been described in similarly-designed BPH studies with finasteride.

Evidence from both human and animal studies shows that development, growth, function, and maintenance of the prostate gland are primarily androgen dependent [Tindall, 2008]. DHT is the principle androgen responsible for normal and hyperplastic growth of the prostate, including both BPH and prostate cancer. DHT is formed from testosterone by the enzyme 5α-reductase of which two forms exist: Type 1 and Type 2. Type 2 predominates in benign prostate tissue, whereas Type 1 is increased in prostate cancer. Male pseudohermaphrodites with 5α-reductase type 2 deficiency have immature prostates and undetectable PSA [Imperato-McGinley, 1992], and prostate cancer has not been seen in males with this condition [Newling, 1995]. Therefore, DHT suppression may inhibit malignant transformation in the prostate and alter the natural history of existing prostate cancer.

A basic science program examined the role of dutasteride in prostate cancer treatment and key findings are:

- Type 1 5α-reductase is over-expressed in prostate cancer cell lines and human prostate cancer tissue compared to benign tissue and the expression is greater in high-grade compared with low-grade prostate cancer [Thomas, 2008].

- Dutasteride reduces cell viability and proliferation and induces changes in gene expression consistent with androgen deprivation in human prostate cancer cells [Schmidt, 2004].

- Dutasteride has been shown to be more effective than finasteride, a Type 2-specific inhibitor, at suppressing the growth of prostate cancer in both animal and human models of prostate cancer.

    - In human primary cultures of prostate cancer cells, dutasteride was more effective than finasteride at reducing the growth of explants of human prostate cancers [Festuccia, 2008]. Whereas finasteride efficacy was dependent upon a high ratio of Type 2:Type 1 5α-reductase, dutasteride's efficacy was independent of the relative amounts of the two enzymes.

    - In another study, treatment of rats with finasteride reduced normal prostate weight and DHT levels, but did not decrease prostate cancer growth or DHT levels in Dunning R-3327 rats. Dutasteride reduced both normal and malignant growth and DHT concentrations [Xu, 2006].

Dutasteride decreases serum and intraprostatic DHT by >90%. This decrease is accompanied by a 15 to 20% increase in serum testosterone and the total serum androgen level is unchanged [Rittmaster, 2008]. In Study AIRA10009, a 1-year, placebo-controlled study of dutasteride 0.5 mg once daily in healthy male volunteers, there were no clinically significant changes in levels of sex-hormone binding globulin (SHBG), haemoglobin (Hgb), or bone density, which would typically be seen in hypogonadal males [Amory, 2008]

1.4. Clinical Development Program

In 2002, a clinical program was initiated to investigate the safety and efficacy of dutasteride for reduction in the risk of biopsy-detectable prostate cancer (Table of Studies Appendix A Section 12.1).

GlaxoSmithKline (GSK) designed the pivotal study, ARI40006 (REDUCE), in consultation with urologists and regulatory authorities from the EU and the FDA to provide long-term (4-year) data in men with known risk factors for prostate cancer (Section 1.5).

ARI103094, a 2-year ongoing observational follow-up study to REDUCE, was initiated in April 2009, with final results to be available in mid 2011.

Supportive safety data are provided by Study ARI40005 (CombAT), which investigated the use of dutasteride treatment alone or in combination with the alpha blocker tamsulosin in male subjects with moderate to severe symptomatic BPH. The same dutasteride dosage regimen as in REDUCE (0.5 mg once daily for 4 years) was used in the dutasteride monotherapy arm of CombAT.

AVO105948 (REDEEM) is a study which investigated the use of dutasteride (0.5 mg once daily for 3 years) or placebo treatment in male subjects diagnosed with low-risk, localized prostate cancer who were candidates for or undergoing expectant management. Expectant management is defined as actively monitoring the course of disease with the expectation to intervene if the cancer progresses or if symptoms become imminent [National Comprehensive Cancer Network, 2005]. The study was completed and results became available in August 2010, after the sNDA for reduction of risk of biopsy-detectable prostate cancer in men at risk for prostate cancer was submitted. REDEEM data is relevant to the discussion around dutasteride and high grade cancers and provides additional insights into dutasteride mechanism of action and its potential impact on the rates of tumor progression and upgrading or reclassification over 3 years compared to placebo in a population with low risk prostate cancer that shared similar characteristics to those diagnosed of Prostate Cancer in REDUCE.

1.5. Regulatory Interactions

No specific regulatory guidelines or precedents were available to guide the conduct of clinical studies for reducing the risk of prostate cancer when REDUCE was designed. The study was developed with input from international urologists and experts in prostate cancer and it was reviewed and approved by the REDUCE Steering Committee, which was comprised of experts external to GSK. In 2002, the study design was discussed with the FDA and 4 European regulatory agencies (Sweden, France, Germany and the UK) to support potential worldwide registration. The study was discussed with the FDA during a meeting with the Division of Reproductive and Urologic Drug Products (DRUDP) on September 5, 2002 with 2 follow-up teleconferences in October and November, 2002. The study design that was agreed on is described in Section 2.1. There was discussion that the p-value for a single study would have to be small and the actual difference between drug and placebo groups would have to be clinically compelling. DRUDP agreed to a significance level of 0.01 at the 4-year analysis.

Based on a request from the FDA Division of Drug Oncology Products (DDOP) at a teleconference in December 2008, complete 4-year safety data from CombAT are included in the sNDA application. CombAT evaluated the same dosing regimen (0.5 mg once daily for 4 years) of dutasteride as REDUCE in men aged 50 years or older with moderate to severe symptomatic BPH. In addition, prostate cancer data reported as AEs in CombAT are included to help elucidate the effect of dutasteride in a BPH population of men who were screened annually with serum PSA and a digital rectal exam, and in whom only for-cause biopsies were done.

On March 26, 2010, GSK submitted a supplemental NDA (sNDA) to NDA 21-319 to DDOP for AVODART (dutasteride) for the reduction of risk of prostate cancer. Completed data from REDUCE and CombBAT were included in the submission.

Limited data available from ARI103094, the ongoing 2-year observational follow-up study for REDUCE, initiated in April 2009 were included in the application.

Regulatory Interactions Subsequent to Submission of sNDA:

- May 2010: A "45-day meeting," Sponsor Orientation Meeting was held with FDA DODP where GSK presented an overview of the sNDA submitted in March 2010.

- June 2010: A teleconference was held with FDA DODP to discuss GSK plans to have prostate cancer biopsy slides reread and scored according to the ISUP 2005 modified Gleason scoring method (see Appendix C Section 12.3 for description of Gleason scoring methods). A Charter for the reread was submitted to FDA following discussion and agreement at the teleconference.

- July 2010: GSK submitted the 120-Day Safety Update to the sNDA.

- September 2010: GSK submitted near complete results of the re-read of prostate cancer biopsy slides and a summary of the recently completed study AVO105948 (REDEEM), a randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of dutasteride in extending the time to progression of low-risk, localized prostate cancer in men who are candidates for or undergoing expectant management.

Other Regulatory Milestones for dutasteride:

- November, 2001: Approval of dutasteride for treatment of BPH in the US.

- June, 2008: Approval of application containing 2-year data from CombAT for dutasteride (0.5 mg daily), tamsulosin (0.4 mg daily), or combination of dutasteride and tamsulosin administered to men diagnosed with BPH in the US.

- March, 2010: Submission of application containing 4-year data from CombAT for dutasteride (0.5 mg daily), tamsulosin (0.4 mg daily), or combination of dutasteride and tamsulosin administered to men diagnosed with BPH.

1.5.1. Proposed Indication and Dosing

Based on the Phase III pivotal study reported in this submission, the proposed indication is:

"AVODART is indicated for reduction in the risk of prostate cancer in men at increased risk of developing the disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA)."

The recommended dosage and administration in this indication is one 0.5 mg capsule given once daily and is identical to that currently approved.

2. PIVOTAL STUDY ARI40006: REDUCE

2.1. Study Design and Methodology

REDUCE was a Phase III, international, multicenter, randomized, double-blind, placebo-controlled, parallel group study. It was designed to evaluate the efficacy and safety of oral, once daily dosing of 0.5 mg of dutasteride for 4 years in reducing the risk of biopsy-detectable prostate cancer in men considered to be at increased risk for prostate cancer. Eligible subjects completed a 4-week placebo run-in phase followed by randomization, by center, to either 0.5 mg dutasteride or matching placebo in a 1:1 ratio for a 4-year treatment phase. After the treatment phase, subjects entered a 4-month safety follow-up phase. The total study duration for each subject, including the placebo run-in phase was up to 53 months.

In order to maintain investigator blinding to study treatment, PSA results of subjects treated with dutasteride were adjusted by doubling the actual value by 2 from 6 months onwards. Investigators were blinded to DHT and T results of all randomized subjects.

2.1.1. Rationale for REDUCE Study Design

The study required that subjects had a negative prostate biopsy prior to enrolling and 2 study-mandated biopsies at Year 2 and Year 4 of the study. The prior negative biopsy indicated that the physician had a clinical concern about prostate cancer. Also, the required entry biopsy excluded men with large aggressive tumors who might be least likely to benefit from dutasteride. The protocol-mandated biopsies at 2 and 4 years of treatment were an important part of the REDUCE study design. Because dutasteride causes decreases in PSA levels, and PSA change is the usual trigger for prostate biopsies, the required biopsies ensured that all subjects were evaluated for the primary endpoint, having an equal chance of being diagnosed with cancer during the course of the study.

These protocol-mandated or scheduled biopsies insured that prostate cancer detection would be independent of PSA levels. If PSA-triggered biopsies were decreased by dutasteride, it might be expected that a lower number of subjects treated with dutasteride compared with subjects treated with placebo would be assessed or biopsied. For-cause biopsies, unscheduled and for clinical concern, were permitted, if clinically indicated. However, avoiding large numbers of for-cause biopsies driven by PSA, would allow us to determine if changes in PSA truly predict the likelihood of cancer. PSA levels were routinely doubled in reports to investigators so that they were blinded to subjects' treatment.

An elevated PSA of 2.5 ng/mL was considered a risk factor for prostate cancer, particularly in the absence of severe BPH. This was established as a lower limit for inclusion for men considered to be at risk of prostate cancer, and the upper limit of 10ng/ml excluded men with severe BPH who might not be able to make it through the study duration without prostate treatment or surgery.

The age range for inclusion of 50-75 years of age was chosen based on the elevated risk of prostate cancer detection during these years, and to avoid biopsy and aggressive

treatments in men over 75 who are unlikely to die from a new diagnosis of prostate cancer.

2.1.2. Dose Rationale

The registered dose (0.5 mg once daily) in men with BPH was used in REDUCE because it has demonstrated:

1. a reduced incidence of prostate cancer in the pivotal BPH studies compared to placebo that was based on a retrospective review of adverse event data
2. a consistent safety and tolerability profile in a similar patient population
3. similar DHT suppression to that achieved with higher doses

2.1.3. Study Conduct

After screening and baseline visits, subjects were asked to visit the clinic every 6 months. They were contacted by telephone at 6-month intervals starting at Month 3. Efficacy assessments at clinic visits included:

- serum PSA, blood protein biomarkers, and health outcomes at baseline and every 6 months. Health outcomes were assessed using questionnaires that evaluated the impact on quality of life (QOL) of BPH, of prostatitis symptoms (urinary symptoms and pain), assessment of sexual function, and evaluation of sleep and its quality every 6 months.
- urinary flow at screening at all sites and every 12 months at selected sites
- Prostate biopsies by transrectal ultrasound (TRUS) every 24 months for protocol-dependent biopsies
- Prostate volumes by TRUS prior to randomization and every 24 months
- histopathological assessments based on biopsies and surgical resection specimens
- postbiopsy macroscopic hematuria and hematospermia, UTI

Pharmacodynamic assessments included serum DHT and testosterone at screening and every 12 months

Safety evaluations included:

- adverse events (AEs) and serious adverse events (SAEs) at each clinic visit and telephone contact, i.e., every 3 months
- serum total PSA every 6 months
- clinical chemistry, hematology, vital signs, digital rectal examination (DRE), gynecomastia evaluations every 12 months

- Post void residual volume (PVRV) and electrocardiogram (ECG) once prior to the start of treatment in order to determine eligibility

- Partner pregnancies throughout

- Concomitant medications at each clinic visit and telephone contact, i.e., every 3 months

The disease being studied or signs/symptoms associated with the disease or disorder were not considered AEs (or SAEs) unless they were more severe than expected for the subject's condition (e.g., prostate cancer, High Grade Prostatic Intraepithelial Neoplasia [HGPIN]).

Randomized subjects who were withdrawn from the study were required to complete the end of treatment assessments. This was followed by a safety follow-up telephone call 4 months after the last dose of study drug. In addition, if subjects consented, investigators contacted them by telephone every 6 months for the remainder of the "4 year treatment period" for collection of specified clinical events.

Subjects who were diagnosed with prostate cancer permanently discontinued study drug and had end of treatment assessments; however, they were not required to be withdrawn from the study. Hence, these subjects could be off-treatment, but still considered on-study. They returned for clinic visits for modified assessments and procedures every 6 months based on the original randomization schedule.

2.1.3.1. Prostate Biopsies

Subjects were required to have a single negative prostate biopsy within 6 months prior to randomization, and two study-defined scheduled biopsies at treatment Year 2 and Year 4. A minimum of 6 cores and a maximum of 12 cores were required for entry biopsies.

The single negative baseline biopsy of 6-12 cores was required (outside of the study) for entry into the study to ensure that the referring physicians considered that the participants were of clinical concern, at increased risk of prostate cancer.

The protocol-defined 10-core biopsies were mandated at Year 2 and Year 4 to ensure that all participants had an equal chance of being evaluated for their prostate cancer status. To the best extent possible, protocol-independent (for-cause) biopsies (during the first 18 months and between months 25 and 42) were discouraged to minimize ascertainment bias. Such a bias could occur if dutasteride, because it decreases PSA, a main driver of for-cause biopsies, resulted in less frequent for-cause biopsies being done and cancer status assessed in fewer subjects than in the placebo group. The conclusion could then be that there were fewer cancers compared with placebo without an evaluation of the whole study population.

Unscheduled (for-cause) biopsies could be performed at any time at the discretion of the investigator if clinically indicated. If a for-cause biopsy was done within 6 months before the scheduled Year 2 or Year 4 study-defined biopsy, then the for-cause biopsy replaced the corresponding study-mandated scheduled biopsy. Central Pathology

conducted primary review of study mandated biopsies and confirmatory review of other biopsies. The definitions of the biopsy types are:

Recording of Biopsy TYPE: All needle biopsy procedures during the treatment phase of the trial were identified by the investigator as one of 3 potential types of biopsy: (a) 2 year scheduled biopsy or (b) 4 year scheduled biopsy or (c) unscheduled biopsy. A procedure date was also recorded for each biopsy and was used in determining if a biopsy was protocol dependent or protocol independent.

Protocol-Dependent Biopsy: A protocol-dependent biopsy was based strictly on a procedure date that occurred during the protocol defined windows of 6 months prior to the scheduled 2 year or 4 year biopsies. These were defined as "After month 18 to end of year 2" for year 2 biopsy, and "After month 42" for year 4 biopsy.

Protocol-Independent Biopsy: A protocol-independent biopsy was based strictly on a procedure date that occurred outside of the protocol defined windows. These were defined as "Treatment start to month 18" and "Start of Year 3 to Month 42".

For-Cause (Unscheduled) Biopsy: A for-cause biopsy was done for clinical concern and was identified based on the **type** of procedure as recorded by the Investigator. Such biopsies could be either protocol-independent or protocol-dependent. Protocol-independent needle biopsies were considered to be for-cause biopsies. Depending on the procedure date, a for-cause biopsy could be classified as a protocol-dependent biopsy.

Appropriate steps were taken to thoroughly evaluate cases of biopsy-detectable prostate cancers, HGPIN, ASAP, and prostate surgeries that arose during the study. These steps included requiring a standard TRUS-guided 10-core biopsy with a pre-defined pattern, and primary and confirmatory reviews of protocol-dependent and protocol-independent biopsies, respectively by a central pathology laboratory. To ensure consistency of diagnosis and Gleason scoring (see Appendix C Section 12.3 for description), all cases positive for prostate cancer, HGPIN and ASAP and all prostate surgeries were reviewed by the lead pathologist, Dr. David Bostwick (Bostwick Laboratories, Glen Allen, Virginia), considered an expert in the field. In addition, an external pathologist provided concurrent review of 200 study biopsy results in order to evaluate the consistency of diagnostic results from the central pathology laboratory.

The Gleason scoring at diagnosis was done by Bostwick Laboratories using the classic Gleason scoring system and hence, all Gleason score data in the sNDA application for Prostate cancer risk reduction are derived from this method. These results are presented in Section 3.2.1 and Section 3.2.2. Because of concerns that the classic Gleason scoring system might under-report the presence of high grade cancers (Gleason 7-10), at the request of FDA, cancers detected during the study were re-evaluated after the conclusion of the study using the IUSP 2005 modified Gleason scoring system [Epstein, 2005]. These included available positive diagnostic or representative slides from the initial protocol-dependent biopsies for first-time positive cancer diagnosis as diagnosed by Bostwick Laboratories. Protocol-independent biopsies were also reread (see Appendix C Section 12.3 for description of the two methods, and the reread methodology). Dr. Scott Lucia was the independent pathologist who performed the rereads. Details of scores obtained by the modified method are presented in Section 3.4.

The classic *Gleason system* was used to grade the tumors of subjects in the REDUCE trial. Lower Gleason scores describe well-differentiated, less aggressive tumors. Higher scores describe poorly differentiated, more aggressive tumors (see Appendix C Section 12.3 for additional details). The classic Gleason scoring system is based solely on the architectural pattern of the tumor: A Gleason grade (pattern) of 1 to 5 is assigned to the 1st and 2nd most predominant patterns present in >5% of the tumor specimen and the grades are added together to obtain the Gleason score. The grade for the primary pattern is doubled if this pattern was present in ≥95% of the specimen. The presence of a 3rd pattern is not considered in the overall Gleason score calculation. From a practical perspective, Gleason grades 1 and 2 are rarely used to describe cancers in biopsy specimens. Therefore, the lowest Gleason score commonly present on biopsies is Gleason 6 (3+3).

In 2005, The International Society of Urological Pathology (ISUP) modified the classic Gleason scoring (modified Gleason scoring methodology) so that: the predominant pattern in the specimen is classified as the primary overall grade. The existence of any higher Gleason pattern, regardless of volume, is classified as the overall secondary grade, and added to the primary grade. Secondary patterns present in <5% of the total cancer are included in the modified consensus scoring approach. Large cribriform glands are classified as Gleason pattern 4 (previously classified as Gleason pattern 3).

2.1.4. Eligibility Criteria

The study recruited males aged between 50 and 75 years (≤71 years in France) at increased risk of prostate cancer defined as having an elevated PSA value (≥2.5 ng/mL and ≤10 ng/mL for men aged ≥50 to ≤60 years, or ≥3.0 ng/mL and ≤10 ng/mL for men aged >60 to ≤75 years) and having a single negative prostate biopsy of 6 to 12 cores in the preceding 6 calendar months. A biopsy was categorized as negative if prostate cancer and atypical small acinar proliferation (ASAP) were absent. All men must have had a single negative prostate biopsy, independent of the study within 6 months preceding enrolment.

Men with evidence of ASAP or high grade prostatic intraepithelial neoplasia (HGPIN) at baseline were also excluded to minimize the likelihood of early for-cause biopsies. Due to the difficulty of adequately sampling large prostates with a 10-core biopsy, subjects entering the study had to have a prostate volume of 80 cc or less. The study was also designed to minimize enrollment of men who may have been candidates for BPH-related surgery by excluding men with previous prostate surgery, severe prostatism (International prostate symptom score [IPSS] of ≥25) and peak flow rates (Qmax) below 5 mL/sec. In addition, alpha-blockers were allowed to control BPH symptoms.

2.1.5. Primary, Secondary and Other Key Endpoints

The primary efficacy endpoint was biopsy-detectable prostate cancer after 2 and 4 years of treatment. Statistical significance was considered at α=0.001 for the 2-year analysis and α=0.01 for the final analysis. As agreed with regulatory authorities, more stringent

levels of significance than usual were required because of the absence of a second confirmatory study.

In order to explore the characteristics of prostate cancers detected during the study, the following secondary endpoints were included: Gleason score at diagnosis, HGPIN at diagnosis, the number of cancer positive cores and the percentage of cores with prostate cancer at diagnosis, treatment alteration scores, intervention for prostate cancer and overall survival. Other prostate cancer endpoints included ASAP and cancer volume.

REDUCE also examined the effect of dutasteride on BPH and prostatitis endpoints. BPH endpoints included prostate volume, IPSS, maximum urine flow, use of alpha-blockers, incidence of acute urinary retention (AUR), urinary tract infections (UTIs) and post-biopsy macroscopic hematuria and hematospermia. Common preventive and management strategies may apply for both diseases [Alcaraz, 2009]. PSA is a recognized risk factor for prostate cancer development as well as a risk factor for BPH progression [Emberton, 2003] and is also increased in other benign inflammatory or infectious conditions such as prostatitis.

2.1.6. Major Protocol Amendments

The original protocol was approved on 08 November 2002.

There were four substantial amendments applicable to all countries with subjects enrolled. These amendments included, but were not limited to, the addition of histopathological review of prostate surgery tissue, revision and clarification of entry criteria (PSA, free PSA, post-void residual volumes, excluded medications), addition of a prostate cancer follow-up arm to the study for subjects diagnosed with prostate cancer, and clarification of the definitions for "subject completion" for the purpose of efficacy analysis. For a listing of all protocol amendments, refer to Appendix B Section 12.2.

2.1.7. Statistical Analysis

The primary endpoint of the study was time to biopsy-detectable prostate cancer. With S_{dut} and S_{pbo} representing the distribution of time to biopsy-detectable prostate cancer for the two treatment groups, then the null and alternative hypotheses tested were that $S_{dut}=S_{pbo}$ or that $S_{dut}\neq S_{pbo}$, respectively.

After 2 years and 4 years of treatment, a 12.5% and 19% cumulative incidence of subjects with prostate cancer in the placebo group was assumed and a 10% and 15.2% cumulative incidence of subjects with prostate cancer in the dutasteride group, for a 20% reduction in the risk.

Enrollment of 4000 subjects per treatment group was planned in order to provide 51% power to detect a treatment difference using a two-sided test at the 0.001 significance level after 2 years of treatment and 94% power to detect a treatment difference using a two-sided test at the 0.01 significance level after 4 years of treatment.

The primary comparison of interest was the comparison between the 0.5 mg dutasteride group and the placebo group for grouped time to biopsy-detectable prostate cancer after 2 years and after 4 years of treatment.

The Efficacy Population was the primary efficacy analysis population and consisted of all randomized subjects with a negative entry prostate biopsy as determined by the Central Pathology Laboratory and who received at least one dose of study treatment. The Biopsied Population included all subjects in the Efficacy Population who had at least 1 post-baseline biopsy reviewed by the Central Pathology Laboratory.

The primary analysis of the primary endpoint at Year 4 was performed using the Mantel-Cox test (i.e., the life-table extension of the Mantel-Haenszel test) stratified by site cluster and time period (Year 1-2 and Year 3-4). Relative risk (0.5mg dutasteride treatment vs. placebo), relative risk reduction, and 95% confidence intervals for the relative risk reduction were computed based on the Mantel-Haenszel estimate of the relative risk.

Protocol-dependent biopsies were those occurring "after month 18 to end of year 2" (counted as the Year 2 biopsies) and those occurring "after month 42" (counted as the Year 4 biopsies). Biopsies were considered protocol-independent if they occurred during the following time intervals: "treatment start to month 18 or "start of year 3 to month 42." For-cause biopsies were unscheduled and were performed for clinical concern. Depending on the procedure date, a for-cause biopsy could be classified as a protocol-independent or protocol-dependent biopsy (see Section 2.1.3.1).

Three different methods were used to analyze the data from REDUCE (Table 5).

Table 5 REDUCE: Crude Rate, Modified Crude Rate and Restricted Crude Rate Definitions (Efficacy Population)

Data Analysis Approach	Population Represented	Denominator[a]		
		Year 1-2	Year 3-4	Year 1-4
Crude Rate	ITT	All Subjects	Negative Biopsy after Month 18 or Biopsy during Years 3-4	All Subjects
Modified Crude Rate	"Completers"	Positive Biopsy Years 1-2 or Biopsy after Month 18	Positive Biopsy Years 3-4 or Biopsy after Month 42	Positive Biopsy Years 1-4 or Biopsy after Month 42
Restricted Crude Rate	Biopsied Population	Biopsy during Years 1-2	Biopsy during Years 3-4	Biopsy during Years 1-4

a. Numerator = Subjects with biopsy-detectable prostate cancer

The primary analysis for determination of risk was performed using the crude rate approach which includes all subjects at risk at the beginning of each time period; i.e. an intent-to-treat approach. Two alternative analyses were conducted to investigate the sensitivity of results to the method of handling of biopsy data: restricted crude rate and modified crude rate analyses. Restricted crude rates were determined by analyzing data from all subjects having at least one biopsy. The modified crude rate analysis was conducted with subjects who either were diagnosed with prostate cancer during the study

or had an end-of-study biopsy. A fourth analysis, including the safety population (all subjects randomized to treatment) was added in accordance with an FDA request.

A limitation of the crude rate is that it assumes that men who were not biopsied do not have prostate cancer. The limitation of the modified crude rate is that it excludes the subjects that had a negative biopsy during the study, but did not have an end of study biopsy.

Statistical analyses of secondary and other key endpoints are specified throughout the results section in table footnotes.

2.2. Study Population

2.2.1. Disposition

A total of 8231 subjects were randomized to treatment with dutasteride (N=4105) or placebo (N=4126) for up to four years. In each group 71% of subjects completed the treatment period. The majority of subjects were from Europe (60%), then the USA/Canada/Puerto Rico (26%) and the Rest of World (14%).

2.2.2. Baseline Demographics and Other Key Baseline Characteristics

Subjects were predominantly White, with a median age of 63.0 years. The treatment groups were balanced at baseline across a wide variety of prostate-related measurements. Median IPSS was 8 in both groups, indicating subjects had mild or moderate lower urinary tract symptoms. Median age, PSA, PSA density and percent free PSA were consistent with a population at increased risk of developing prostate cancer (Table 6).

Table 6 Demography and Baseline Characteristics (REDUCE Safety Population)

Baseline Value	Placebo N=4126	Dutasteride N=4105
Age (median) years	63.0	63.0
Race (%)		
White	91	91
Non-white	9	9
Total PSA (median) ng/mL	5.70	5.70
Percent Free PSA (median)	16.0	16.2
PSA density (median) ng/mL/cc	0.13	0.13
Prostate volume (median) cc	43.4	43.4
Number of Cores Sampled (median)	9.0	9.0
Previous Prostate Cancer Family History (%)	13	13
IPSS (median)	8.0	8.0
Qmax (median) mL/sec	13.3	13.2
Prior use of Alpha Blockers (%)	21	20
Sexually Active (%)	81	81
Impotence in Past 3 Months (%)	28	29
Lack of Libido in Past 3 Months (%)	23	22

The treatment groups were similar in their past and current medical conditions (Table 7).

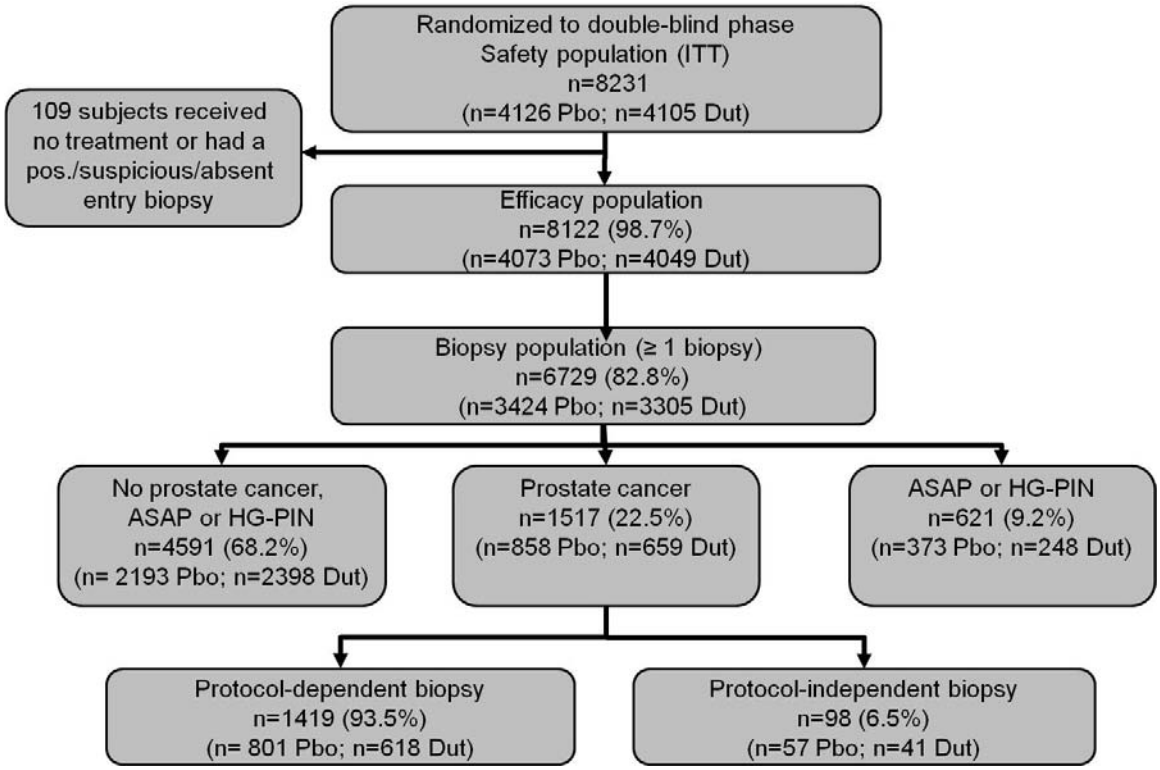
Table 7 Past and Current Relevant Medical Conditions (REDUCE Safety Population)

Medical Condition		Placebo N=4126 n (%)	Dutasteride N=4105 n (%)
Any condition	Past	3585 (87)	3554 (87)
	Current	3880 (94)	3843(94)
BPH	Past	1657 (40)	1615 (39)
	Current	2716 (66)	2720 (66)
Hypertension	Past	1010 (24)	988 (24)
	Current	1569 (38)	1569 (38)
Other cardiovascular	Past	451 (11)	412 (10)
	Current	496 (12)	513 (12)
Other endocrine & metabolic	Past	359 (9)	346 (8)
	Current	555 (13)	530 (13)
Coronary artery disease	Past	382 (9)	369 (9)
	Current	332(8)	334 (8)
Other reproductive	Past	329 (8)	356 (9)
	Current	319 (8)	322 (8)
Diabetes/glucose intolerance	Past	236 (6)	239 (6)
	Current	355 (9)	347 (8)
Peripheral Vascular Disease/Stroke	Past	198 (5)	184 (4)
	Current	118 (3)	98 (2)
Gynaecomastia	Past	23 (<1)	19 (<1)
	Current	13 (<1)	27 (<1)

Subjects may be counted in multiple categories.

A total of 8122 subjects were included in the **Efficacy Population** (all randomized subjects who had a negative entry biopsy, confirmed at the central pathology laboratory, and took at least one dose of study medication) with 6729 subjects (82.8%) having at least one post-baseline biopsy over four years (**Biopsied Population**) (Figure 1). Baseline characteristics of subjects who did not have a biopsy were similar to those who were biopsied. Overall, 1517 (22.5%) subjects who had a biopsy were diagnosed with prostate cancer. Cancer precursor lesions ASAP and/or HGPIN and no prostate cancer were diagnosed in 9% of subjects. Overall, 68.2% of subjects had negative biopsies (i.e. no prostate cancer, ASAP or HGPIN). The biopsy rate in both treatment groups overall was high at 82.8 % Most prostate cancers were diagnosed in protocol-dependent biopsies (93.5%).

Figure 1 REDUCE Study Population



PCa = Prostate cancer
ASAP = Atypical small acinar proliferation
HG- PIN = High grade prostatic intraepithelial neoplasia

3. EFFICACY RESULTS

3.1. Primary Efficacy Endpoint in REDUCE: Risk of Biopsy-Detectable Prostate Cancer

Dutasteride treatment for up to 4 years reduced the relative risk of biopsy-detectable prostate cancer by 23.3% ($p<0.0001$) compared with placebo using the crude rate approach (95% CI: 15.6%, 30.3%). Similar risk reductions were observed when using the restricted crude rate approach (22.8%; 95% CI: 15.2%, 29.8%) and the modified crude rate approach (23.1%; 95% CI: 15.5%, 30.0%; (Table 8, Table 9, and Table 10, respectively).

More subjects in the placebo group than in the dutasteride group were diagnosed with prostate cancer during the study (placebo group: 21.1% and dutasteride group: 16.3%) using the crude rate analysis (Table 8). In both treatment groups, the incidence of prostate cancer was higher in Years 1-2 (14.2% of placebo subjects and 10.7% of dutasteride subjects) than in Years 3-4 (9.9% % of placebo subjects compared with 7.9% of dutasteride subjects).

Persistence in the effect of dutasteride to reduce the relative risk of prostate cancer compared with placebo was observed. The relative risk for dutasteride subjects was consistent throughout the treatment period: 0.76 in Years 1-2, 0.79 in Years 3-4, and 0.77 overall, using the crude rate approach (Table 8). Using the restricted crude rate approach (Table 9) and the modified crude rate approach (Table 10), the relative risk reduction for dutasteride compared with placebo was similar, persistent and sustained with no evidence of tolerance.

Table 8 Biopsy-Detectable Prostate Cancer Incidence and Relative Risk Reduction: Efficacy Population (Crude Rate Analysis)

	Time Period	Placebo N=4073	Dutasteride N=4049
Incidence of Prostate Cancer % (n)	Years 1-2	14.2% (578/4073)	10.7% (435/4049)
	Years 3-4	9.9% (280/2815)	7.9% (224/2844)
	Overall	21.1% (858/4073)	16.3% (659/4049)
Mantel-Cox P-value[a]	Years 1-2	<0.0001	
	Overall	<0.0001	
Relative Risk % [CI][b]	Years 1-2	0.76 (0.67, 0.85)	
	Years 3-4	0.79 (0.67, 0.93)	
	Overall	0.77 (0.70, 0.84)	
Relative Risk Reduction % [CI][c] (Dutasteride vs. Placebo)	Years 1-2	24.3 (15.0, 32.6)	
	Years 3-4	21.2 (6.8, 33.3)	
	Overall	23.3 (15.6, 30.3)	

Crude Rate Analysis: Includes all subjects at risk at the beginning of each time period.

a. P-value vs. Placebo based on Mantel-Cox test with stratification by cluster (and time period for the Overall test).
b. Estimate is the Mantel-Haenszel relative risk; the confidence interval is based on the Greenland and Robins variance estimate.
c. Estimates computed as 100*(1 - Relative Risk).

Table 9 Biopsy-Detectable Prostate Cancer Incidence and Relative Risk Reduction: Efficacy Population (Restricted Crude Rate Analysis)

	Time Period	Placebo N=4073	Dutasteride N=4049
Incidence of Prostate Cancer %(n)	Years 1-2	17.2% (578/3364)	13.4% (435/3244)
	Years 3-4	11.9% (280/2359)	9.1% (224/2451)
	Overall	25.1% (858/3424)	19.9% (659/3305)
Mantel-Cox P-value[a]	Years 1-2	<0.0001	
	Overall	<0.0001	
Relative Risk % [CI][b]	Years 1-2	0.78 (0.69, 0.87)	
	Years 3-4	0.76 (0.65, 0.90)	
	Overall	0.77 (0.70, 0.85)	
Relative Risk Reduction % [CI][c] (Dutasteride vs. Placebo)	Years 1-2	22.4 (13.0, 30.8)	
	Years 3-4	23.7 (9.9, 35.3)	
	Overall	22.8 (15.2, 29.8)	

Restricted Crude Rate Analysis: Includes all subjects having at least one biopsy.

a. P-value vs. Placebo based on Mantel-Cox test with stratification by cluster (and time period for the Overall test).
b. Estimate is the Mantel-Haenszel relative risk; the confidence interval is based on the Greenland and Robins variance estimate.
c. Estimates computed as 100*(1 - Relative Risk).

Table 10 Biopsy-Detectable Prostate Cancer Incidence and Relative Risk Reduction: Efficacy Population (Modified Crude Rate Analysis)

	Time Period	Placebo N=4073	Dutasteride N=4049
Incidence of Prostate Cancer %(n)	Years 1-2	17.4% (578/3319)	13.6% (435/3209)
	Years 3-4	12.0% (280/2325)	9.2% (224/2434)
	Overall	29.6% (858/2903)	23.0% (659/2869)
Mantel-Cox P-value[a]	Years 1-2	<0.0001	
	Overall	<0.0001	
Relative Risk % [CI][b]	Years 1-2	0.77 (0.69, 0.87)	
	Years 3-4	0.76 (0.64, 0.89)	
	Overall	0.77 (0.70, 0.84)	
Relative Risk Reduction % [CI][c] (Dutasteride vs. Placebo)	Years 1-2	22.6 (13.2, 30.9)	
	Years 3-4	24.2 (10.6, 35.8)	
	Overall	23.1 (15.5, 30.0)	

Modified Crude Rate Analysis: Includes subjects who either were diagnosed with prostate cancer during the study or had an end-of-study biopsy.

a. P-value vs. Placebo based on Mantel-Cox test with stratification by cluster (and time period for the Overall test).
b. Estimate is the Mantel-Haenszel relative risk; the confidence interval is based on the Greenland and Robins variance estimate.
c. Estimates computed as 100*(1 - Relative Risk).

In addition to the 3 efficacy analyses, another analysis was conducted in the safety population that included the 109 subjects who were excluded from the primary analysis because they received no study medication and/or their pre-study biopsy was positive, suspicious, or absent (Figure 1). When these subjects were included, dutasteride treatment for up to 4 years reduced the relative risk of biopsy-detectable prostate cancer by 23.3% ($p<0.0001$) compared with placebo using the crude rate approach (95% CI: 15.7%, 30.3%).

The number needed to treat (NNT) for prostate cancer risk reduction was 19 [95% CI: 13.9, 30.4] (i.e., it is expected that 19 subjects would need to be treated with dutasteride for four years in order to prevent one diagnosis of prostate cancer) for any of the populations analyzed.

3.1.1. Timing and Number of Biopsies

The biopsy rate in both treatment groups overall was high (84.1% of subjects in the placebo group and 81.6% of subjects in the dutasteride group). The majority of needle biopsies (≥94% in each treatment group) performed in the study were protocol-dependent biopsies (those biopsies occurring during the defined study biopsy periods). The protocol-independent biopsy rate was low and relatively constant during the study (Table 11). Protocol-independent and protocol-dependent biopsies are defined in Section 2.1.3.1.

The biopsy rate in the dutasteride group was lower than that in the placebo group prior to Month 42. This is hypothesized to be related to the higher rate of withdrawal from the study by subjects in the dutasteride group due to drug-related AEs. The biopsy rate in the placebo group was lower than that in the dutasteride group after Month 42 (Table 11).

This is hypothesized to be related to the higher rate of earlier prostate cancer diagnosis in the placebo group (and the resulting withdrawal from study drug) during Years 1-2 (Table 12).

Table 11 Time to Post-baseline Biopsies (Efficacy Population)

	Subjects Undergoing Post-baseline Biopsy	
	Placebo N=4073	Dutasteride N=4049
Time Period	n (%)	n (%)
Treatment Start to Month 18[a]	194 (4.8)	166 (4.1)
After Month 18 to end of Year 2	3295 (80.9)	3181 (78.6)
Start of Year 3 to Month 42 [a]	272 (6.7)	178 (4.4)
After Month 42	2307 (56.6)	2431 (60.0)
Overall	3424 (84.1)	3305 (81.6)

a. Protocol –independent biopsies.

For both treatment groups, most prostate cancers were diagnosed from protocol -dependent biopsies in Years 1-2; comparatively fewer prostate cancers were diagnosed in Years 3-4. Fewer than 100 (6.5% of all cancers) subjects were diagnosed with prostate cancer from protocol-independent biopsies throughout the four years of the study (Table 12).

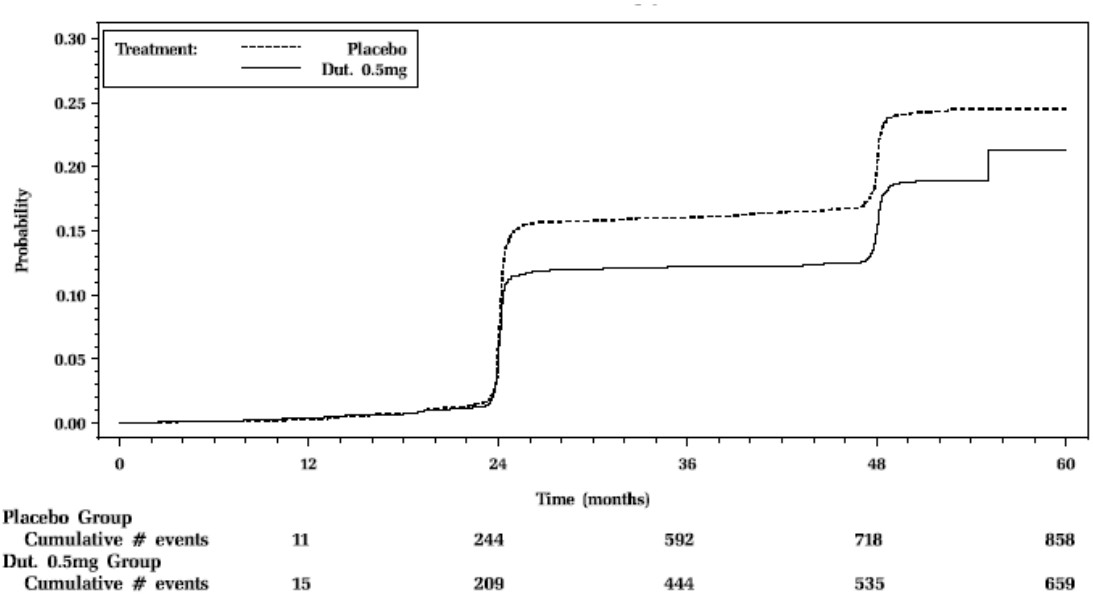
Table 12 Time to First Diagnosis of Prostate Cancer From Biopsies (Efficacy Population)

	Subjects With Prostate Cancer	
	Placebo N=4073	Dutasteride N=4049
Time Period	n (%)	n (%)
Treatment Start to Month 18 [a]	29 (0.7)	29 (0.7)
After Month 18 to end of Year 2	549 (13.5)	406 (10.0)
Start of Year 3 to Month 42 [a]	28 (0.7)	12 (0.3)
After Month 42	252 (6.2)	212 (5.2)
Overall	858 (21.1)	659 (16.3)

a. Protocol –independent biopsies

The cumulative incidence curves for time to biopsy-detectable prostate cancer indicate a lower risk for the dutasteride group than for the placebo group. Since the vast majority of the biopsies were done at Year 2, the curves first diverge at 24 months and incidence remains lower in the dutasteride group throughout the remainder of the study (Figure 2).

Figure 2 Cumulative Incidence Estimates of Time to Biopsy Detectable Prostate Cancer (Efficacy Population)



Note: The increase in prostate cancer present at Month 55 in the dutasteride treatment group is the result of a single case occurring when only 35 subjects on dutasteride were left in the study

3.1.1.1. Prostate Cancer Diagnosed from For-Cause Needle Biopsies

Among the subjects with for-cause needle biopsies, whether they were protocol-dependent or protocol-independent, there were fewer biopsy-detected cancers in the dutasteride group compared with the placebo group (Table 13). The incidence ratio (relative risk) for all for-cause biopsies (0.74) was similar to protocol-independent biopsies (0.79) and all needle-biopsies (0.78).

Table 13 Number of Subjects With Biopsy-Detectable Prostate Cancer Based on For-Cause Biopsy (Protocol-Dependent or Protocol-Independent) (Efficacy Population)

Biopsy Type	Placebo N=4073 n (%)	Dutasteride N=4049 n (%)	Incidence Ratio (95% CI)
All needle biopsies	850 (20.9)	657 (16.2)	0.78 (0.71, 0.85)
For–cause biopsies	86[a] (2.1)	63 (1.6)	0.74 (0.53 1.02)
Protocol-independent biopsies	51 (1.3)	40 (1.0)	0.79 (0.52 1.19)
Both for-cause and protocol -independent biopsies	51 (1.3)	40 (1.0)	0.79 (0.52 1.19)
Either for-cause or protocol -independent biopsies	86[a] (2.1)	63 (1.6)	0.74 (0.53, 1.02)

Incidence Ratio=non-stratified ratio of the incidence values
For-cause biopsy=unscheduled biopsy=protocol independent and/or protocol dependent biopsy.
For-cause biopsy is designated as *protocol-dependent biopsy* if it occurs within 6 months prior of the protocol mandated 2- and 4- Year biopsy period.
For-cause biopsy is designated as *protocol-independent biopsy* if it is outside of the protocol mandated 2- and 4-Year protocol mandated biopsy period.
a. One subject in placebo group had prostate cancer diagnosed by for-cause surgical biopsy followed 2 months later by needle biopsy.

The majority of for-cause biopsies in both treatment groups were performed as a result of a rising PSA (placebo: 72/85, 85%; dutasteride: 49/63, 78%). More prostate cancers were diagnosed from for-cause biopsies than from surgery (placebo: 9 subjects; dutasteride: 2 subjects). Section 3.2.1.6 contains additional data on for-cause biopsies.

When only protocol dependent biopsies were considered, dutasteride treatment reduced the relative risk of biopsy-detectable prostate cancer by 23.4% ($p<0.0001$) compared with placebo using the crude rate approach (95% CI: 15.4%, 30.6%) over 4 years.

3.1.2. Prostate Volume and Effect on Prostate Cancer Diagnosis

The likelihood of diagnosing prostate cancer with a prostate biopsy is known to increase as prostate volume decreases [Basillote, 2003; Kulkarni, 2006]. At Year 2, the adjusted mean prostate decreased by 17.4% in the dutasteride group, but increased in the placebo group by 13.0%, resulting in an adjusted mean difference between treatments in percentage change from baseline of -30.4% (p<0.0001). At Year 4, the adjusted mean prostate volume decreased by 17.5% in the dutasteride group but increased in the placebo group by 19.7%, resulting in an adjusted mean difference between treatments in percentage change from baseline of -37.1% (p<0.0001). The mean prostate volume decreases in the dutasteride group were relatively constant from Year 2 to Year 4 while the mean prostate volume of the placebo group increased. The likelihood of detecting prostate cancer therefore was increased in the dutasteride group relative to the placebo group. (Table 14).

Table 14 Prostate Volume Change from Baseline (Efficacy Population, LOCF)

Time	Prostate Volume (cc)	Placebo N=4073	Dutasteride N=4049
Baseline, n		4001	3969
Baseline	Mean (SD)	45.8 (18.80)	45.7 (17.91)
Year 2, n		3192	3116
	Volume Mean (SD)	52.3 (22.71)	38.6 (17.66)
	Mean %Change from Baseline[a] (SD)	20.2 (48.04)	-12.6 (40.57)
	Adjusted Mean[b] % Change from Baseline (SE)	13.0 (0.65)	-17.4 (0.48)
	p-value	<0.0001	
Year 4, n		3289	3194
	Volume Mean (SD)	56.2 (25.51)	39.0 (18.47)
	Mean % Change from Baseline[a] (SD)	29.0 (57.96)	-11.5 (45.53)
	Adjusted Mean[b] % Change from Baseline (SE)	19.7 (0.77)	-17.5 (0.54)
	p-value	<0.0001	

LOCF=last observation carried forward

a. The percentage change from baseline is 100 * (post-baseline value minus the baseline value, divided by the baseline value).

b. Adjusted for baseline prostate volume

In the biopsied population, subjects in the dutasteride group had smaller prostate volumes at biopsy than placebo subjects (3 times more subjects in the <20 cc category than placebo [383 vs. 109]; 2 times more subjects in the 20 to <30 cc category [966 vs. 431] and 1.5 times the number of subjects in the 30 to <40 cc category [1061 vs. 716]). Although prostate volumes at biopsy were smaller in the dutasteride group than in the placebo group, the overall incidence of prostate cancer was lower in the dutasteride group than in the placebo group within a given prostate volume category (Table 15).

Table 15 Number of Subjects Overall With Prostate Cancer Diagnosis by Prostate Volume At Biopsy (Biopsied Population)

Prostate Volume at Biopsy	Subjects with Prostate Cancer[a] Placebo N=3424 n/n (%)	Dutasteride N=3305 n/n (%)
<20 cc	26/109 (23.9)	70/383 (18.3)
20 to <30 cc	104/431 (24.1)	166/966 (17.2)
30 to <40 cc	144/716 (20.1)	148/1061 (13.9)
40 to <50 cc	140/857 (16.3)	86/790 (10.9)
50 to <60 cc	95/ 777 (12.2)	42/465 (9.0)
60 to <70 cc	78/593 (13.2)	33/266 (12.4)
70 to <80 cc	57/393 (14.5)	11/128 (8.6)
≥80 cc	80/543 (14.7)	4/107 (3.7)
Missing	126/648	97/566

Subjects with multiple biopsies may appear in multiple rows

3.1.3. Subgroup analysis

The reduction of the risk of prostate cancer for subjects in the dutasteride group was consistent irrespective of known risk factors of age, family history of prostate cancer, baseline PSA level, and irrespective of time period and evaluation method (i.e., crude rate, modified crude rate, restricted crude rate). The reduction of risk was seen for the dutasteride group compared with the placebo group for all prostate health-related baseline subgroups (Table 16 and Table 17). With respect to race, the majority of subjects were White (91%), with other ethnic groups comprising ≤4% of the efficacy population. Consequently, prostate cancer relative risk reductions were variable across the Non-White ethnic groups, with wide confidence intervals, making it difficult to make meaningful conclusions.

Table 16 Age and Race Subgroup Analyses of Relative Risk Following Four Years of Treatment (Efficacy Population)

Subgroup	Placebo Incidence N= 4073 n/n[a] (%)	Dutasteride Incidence N= 4049 n/n[a] (%)	Relative Risk Reduction % (95% CI)[b]
Age Category (Years)			
<65	462/ 2410 (19.2)	342/ 2395 (14.3)	25.1 (14.5, 34.4)
≥65	396/ 1663 (23.8)	317/ 1654 (19.2)	21.3 (9.7, 31.4)
Race			
White	792/ 3701 (21.4)	593/3696 (16.0)	25.6 (17.8, 32.7)
Black	14/ 95 (14.7)	19/ 88 (21.6)	-52.1 (-196.0, 21.9)
Asian	11/ 67 (16.4)	5/ 66 (7.6)	65.0 (-29.9, 90.6)
American Hispanic	29/ 170 (17.1)	28/ 156 (17.9)	-12.8 (-84.1, 30.8)
Other	12/ 39 (30.8)	14/ 43 (32.6)	13.4 (-74.7, 57.0)

a. Subjects with prostate cancer/Subjects in the subgroup
b. Estimate computed as 100 (1 – Mantel-Haenszel relative risk); the confidence interval is based on the Greenland and Robins variance estimate.

Table 17 Other Subgroup Analyses of Relative Risk Reduction for Prostate-Related Measurements at Baseline Following Four Years of Treatment (Efficacy Population)

Subgroup		Placebo Incidence N= 4073 n/n[a] (%)	Dutasteride Incidence N= 4049 n/n (%)	Relative Risk Reduction % (95% CI)[b]
Family Prostate Cancer History:	Yes	141/ 514 (27.4)	105/ 536 (19.6)	30.7 (11.4, 45.8)
	No	717/ 3559 (20.1)	554/ 3507 (15.8)	22.2 (13.7, 29.9)
Prostate Volume	<36.6cc	350/ 1331 (26.3)	268/ 1326 (20.2)	22.2 (9.9, 32.9)
	36.6 to <51.8cc	250/ 1335 (18.7)	214/ 1322 (16.2)	16.3 (0.6, 29.5)
	≥51.8cc	244/ 1335 (18.3)	169/ 1321 (12.8)	31.3 (17.2, 43.1)
Total PSA (ng/mL)	<4.9	259/ 1410 (18.4)	194/ 1369 (14.2)	22.6 (7.4, 35.3)
	4.9 to <6.8	308/ 1336 (23.1)	239/ 1344 (17.8)	23.4 (10.4, 34.6)
	≥6.8	290/ 1317 (22.0)	225/ 1330 (16.9)	24.4 (11.1, 35.8)
% Free PSA	<13.7	346/ 1383 (25.0)	261/ 1320 (19.8)	22.3 (9.9, 33.0)
	13.7 to <18.6	267/ 1340 (19.9)	213/ 1361 (15.7)	21.6 (7.2, 33.8)
	≥18.6	244/ 1337 (18.2)	184/ 1362 (13.5)	25.9 (11.2, 38.2)
PSA Density (ng/mL/cc)	<0.11	231/ 1344 (17.2)	174/ 1307 (13.3)	25.2 (9.7, 38.0)
	0.11 to <0.16	262/ 1318 (19.9)	209/ 1333 (15.7)	21.4 (6.6, 33.9)
	≥0.16	350/ 1329 (26.3)	267/ 1323 (20.2)	23.7 (11.7, 34.1)
DRE	Normal/ Enlarged	819/ 3905 (21.0)	635/ 3893 (16.3)	22.7 (14.8, 29.8)
	Abnormal	36/ 159 (22.6)	24/ 147 (16.3)	38.5 (-6.9, 64.6)
Testosterone (nmol/L)	<12.32	276/ 1340 (20.6)	205/ 1341 (15.3)	28.0 (14.6, 39.3)
	12.32 to <17.66	271/ 1350 (20.1)	229/ 1345 (17.0)	14.1 (-1.4, 27.2)
	≥17.66	306/ 1356 (22.6)	219/ 1331 (16.5)	28.6 (15.8, 39.4)
DHT (nmol/L)	<0.96	290/ 1381 (21.0)	210/ 1300 (16.2)	23.6 (9.6, 35.4)
	0.96 to <1.51	288/ 1343 (21.4)	222/ 1363 (16.3)	23.7 (9.9, 35.3)
	≥1.51	276/ 1324 (20.8)	220/ 1350 (16.3)	22.8 (8.9, 34.7)
Number of cores at entry biopsy	9 or less	480/ 2058 (23.3)	377/ 2038 (18.5)	21.7 (11.2, 30.9)
	10 or more	376/ 2003 (18.8)	282/ 2000 (14.1)	25.3 (13.6, 35.5)

a. Subjects with prostate cancer/Subjects in the subgroup

b. Estimate computed as 100 (1 – Mantel-Haenszel relative risk); the confidence interval is based on the Greenland and Robins variance estimate.

Geographical subgroups: Europe, USA/Canada/Puerto Rico and the Rest of the World were the three study regions defined by pooling 33 clusters of sites participating in the study across these regions. The majority of subjects in the study were from Europe (60%), followed by USA/Canada/Puerto Rico (26%), and followed by the Rest of the World (14%). The incidence of prostate cancer was lower in the dutasteride group in all regions compared with the placebo group. Prostate cancer relative risk reduction was numerically greater in the European region (25.2%, 95% CI: 15.9, 33.5) compared with USA/Canada/ Puerto Rico (22.8%, 95% CI: 4.9, 37.3) and Rest of the World (13.9%, 95% CI: -12.2, 33.9). The treatment by cluster interaction was not significant.

Medication subgroups: Generally, for each medication subgroup representing medications taken by subjects prior to the study for which there has been some evidence of Prostate cancer risk reduction (salicylates, selenium, vitamin E, statins) or for treatment of BPH (alpha blockers), there was a lower incidence of prostate cancer in the dutasteride group (14.9 % to 16.5%) compared with placebo (20.2% to 22.9%). The relative risk reductions for dutasteride compared with placebo were similar in all

medication subgroups (24.3 to 29.6), with the exception of selenium. Since selenium use was very low (less than 90 subjects in each treatment group), associated results are difficult to interpret and have a high degree of variability.

3.1.4. Covariate Analyses

Certain variables are known to affect the risk of prostate cancer diagnosis, such as age, family history, and number of cores at a previous biopsy. When these baseline covariates were considered in the log-binomial regression model analyses, the relative risk for dutasteride compared with placebo for prostate cancer diagnosis remained 0.77 (Table 18). Increasing age and family history increased the risk of prostate cancer diagnosis, whereas the higher the number of cores at previous biopsy, the lower the risk of cancer diagnosis.

Prostate volume at the time of biopsy is another covariate known to affect the likelihood of getting a positive prostate cancer diagnosis [Kulkarni, 2006]. Lower prostate volumes increase the likelihood of getting a positive prostate cancer diagnosis. When post-baseline prostate volume at the time of biopsy was added to the log-binomial regression model analysis, the relative risk of dutasteride compared with placebo decreased to 0.64, highlighting the effect and relevance of prostate volume at biopsy on the likelihood of a positive cancer diagnosis, as reported in the literature (Table 18). It is acknowledged that use of post-baseline covariates in regression models can result in difficulties in interpretation of results. Hence adjusted treatment effect estimates should be evaluated accordingly.

Table 18 Effect of Baseline and Post-baseline Covariates on Biopsy Detectable Prostate Cancer (Biopsied Population)

Variable	Relative Risk[a] Estimate % (95% CI)	p-value[b]
Baseline		
Treatment (dutasteride vs. placebo)	0.77 (0.70, 0.85)	<0.0001
Time Period (Years 1-2, Years 3-4)	0.71 (0.64, 0.78)	<0.0001
Age (yrs)	1.05 (1.04, 1.06)	<0.0001
Family History of Prostate Cancer	1.39 (1.23, 1.57)	<0.0001
Baseline Prostate Volume (cc)	-	<0.0001
Baseline % Free PSA	-	<0.0001
Prostate Volume x % Free PSA	-	0.0009
Number of Cores at Entry biopsy	0.96 (0.94, 0.98)	<0.0001
Baseline and Post-baseline		
Treatment (dutasteride vs. placebo)	0.64 (0.57,0.72)	<0.0001
Time Period (Years 1-2, Years 3-4)	0.71 (0.63, 0.79)	<0.0001
Age (yrs)	1.05 (1.04,1.06)	<0.0001
Family History of Prostate Cancer	1.41 (1.23, 1.61)	<0.0001
Baseline Prostate Volume (cc)	-	0.0427
Baseline % Free PSA	-	<0.0001
Number of Cores at Entry biopsy	0.96 (0.94, 0.98)	<0.0001
Baseline Prostate Volume x Baseline % Free PSA	-	0.0445
Prostate Volume at latest biopsy (cc)	0.99 (0.99, 0.99)	<0.0001

a. Relative risk is estimated using a log-binomial generalized linear model containing the variables listed above, and are adjusted for all other variables in the model. Estimates are not provided for effects involved in interactions since these are not interpretable on an individual basis

b. Confidence intervals and p-values are computed using the Wald method.

3.2. Secondary Endpoints and Other Key Endpoints in REDUCE

3.2.1. Gleason score at Diagnosis in the Biopsied Population: Classic Gleason Scoring

As noted in Section 2.1.3.1 the Classic method of Gleason scoring was used for grading prostate cancer in the Biopsied Population and these data are presented here. Gleason scores obtained from rereads of the same samples using the 2005 Modified Consensus method for scoring are presented in Section 3.4.

The majority of prostate cancers in both treatment groups in the biopsied population were diagnosed as low grade (Overall Gleason score 2-6) with the vast majority of them being Gleason score 6. The number of low grade cancers detected was higher in Years 1-2 than in Years 3-4 for both treatment groups. At all timepoints, the incidence of low grade cancers was lower in the dutasteride group compared with the placebo group (Table 19).

Overall (Years 1-4), in Years 1-2, and in Years 3-4, the incidence of Gleason score 7-10 cancers in both treatment groups was similar, with the majority of high grade cancers having a Gleason score of 7 (3+4) (Table 19).

Overall (Years 1-4), in Years 1-2, and in Years 3-4, the incidence of Gleason score 8-10 cancers (a subset of high grade tumors) was low. In Years 3-4, although the incidence of Gleason score 8-10 cancers was low in both treatment groups, more Gleason score 8-10 cancers were diagnosed in the dutasteride group (12 subjects) compared with the placebo group (1 subject) (Table 19). Of note, the incidence of Gleason score 8-10 cancers did not change in the dutasteride group over time, from Years 1-2 to Years 3-4, but decreased in the placebo group from Years 1-2 to Years 3-4.

Table 19 Number of Subjects by Overall Gleason Score for Post-baseline Biopsy in REDUCE (Biopsied Population)

	Number of Subjects		
	Placebo N=3424	Dutasteride N=3305	
Overall Gleason score[a]	n[b] (%)	n[b] (%)	p-value[c]
Years 1 – 2	n[b] =3346	n[b] =3239	
2 – 6	401 (12.0)	290 (9.0)	<0.0001
6	398 (11.9)	289 (8.9)	
7 – 10	175 (5.2)	144 (4.4)	0.15
7 (3+4)	125 (3.7)	99 (3.1)	
7 (4+3)	32 (1.0)	28 (0.9)	
8 – 10	18 (0.5)	17 (0.5)	1.0
Years 3 – 4	n[b] =2343	n[b] =2447	
2 – 6	216 (9.2)	147 (6.0)	<0.0001
6	215 (9.2)	147 (6.0)	
7 – 10	58 (2.5)	76 (3.1)	0.19
7 (3+4)	51 (2.2)	47 (1.9)	
7 (4+3)	6 (0.3)	17 (0.7)	
8 – 10	1 (<0.1)	12 (0.5)	0.0035
Overall	n[b] =3407	n[b] =3299	
2 – 6	617 (18.1)	437 (13.2)	<0.0001
6	613 (18.0)	436 (13.2)	
7 – 10	233 (6.8)	220 (6.7)	0.81
7 (3+4)	176 (5.2)	146 (4.4)	
7 (4+3)	38 (1.1)	45 (1.4)	
8 – 10	19 (0.6)	29 (0.9)	0.15

a. The Gleason scores are those assessed at the initial diagnosis of prostate cancer.
b. Denominator is the number of subjects with needle biopsy. Surgery results are excluded.
c. P-value vs. Placebo based on Fisher's exact test.

The difference in Gleason 8-10 cancers in Years 3-4 is discussed in detail in Section 3.2.1.7.

3.2.1.1. Prostate Cancer Relative Risk and Relative Risk Reduction by Gleason Score

Overall, the relative risk (nonstratified ratio of incidence values) of Gleason score 5-10 cancers for dutasteride compared with placebo was 0.80. In Gleason score 7-10 cancers the relative risk was also <1, but increased to 0.98. In Gleason score 8-10 cancers the relative risk increased to 1.58. For Gleason score 7-10 and 8-10 cancers, the 95% confidence interval for the relative risk reduction included zero (Table 20).

The efficacy of dutasteride in relation to the risk reduction was higher in the lower Gleason scores and decreased with increasing Gleason score.

Table 20 Overall Relative Risk of Higher Overall Gleason score (Biopsied Population)

Gleason score[a]	Placebo N=3424 n/n[b] (%)	Dutasteride N=3305 n/n[b] (%)	Relative Risk[c]	Relative Risk Reduction[d] % (95% CI)
	n[b]=3407	n[b]=3299		
5 – 10	850 (24.9)	657 (19.9)	0.80	20.2 (12.7, 27.0)
6 – 10	846 (24.8)	656 (19.9)	0.80	19.9 (12.4, 26.8)
7 – 10	233 (6.8)	220 (6.7)	0.98	2.5 (-16.5, 18.4)
8 – 10	19 (0.6)	29 (0.9)	1.58	-57.6 (-181, 11.4)

a. The Gleason scores are those assessed at initial diagnosis.
b. Denominator is the number of subjects with needle biopsy. Surgery results are excluded.
c. Estimate is the ratio of the incidence values (non-stratified).
d. Estimates computed as 100(1-Relative Risk). Confidence interval based on that for the relative risk using the Wald method for the log of the incidence ratio.

3.2.1.2. Covariate Analysis for High Grade Cancers (Gleason score 7-10)

Covariate analysis results for the occurrence of Gleason score 7-10 cancers are presented using logistic models since the log-binomial models did not converge; therefore only the results of the logistic regression model are presented here.

Certain variables are known to affect the risk of prostate cancer diagnosis, such as age, family history, and number of cores at a previous biopsy. When these baseline covariates were considered in logistic regression model analyses, the odds ratio for the treatment effect for the occurrence of high-grade cancers (Gleason score 7-10) decreased from 0.98 (unadjusted) to 0.92 (Table 21). Increasing age and family history increased the risk of high grade prostate cancer diagnosis, whereas the higher the number of cores at entry biopsy the lower the risk of high grade cancers diagnosed.

When post-baseline prostate volume at the time of biopsy was added to the logistic regression model analysis, the odds ratio of dutasteride compared with placebo for Gleason 7-10 cancers decreased from 0.92 (p=0.42) to 0.62 (p=0.0001), highlighting the effect and relevance of prostate volume at biopsy on the likelihood of high grade prostate cancer diagnoses, as reported in the literature [Kulkarni, 2006]. As previously noted, use of post-baseline covariates in regression models can result in difficulties in interpretation of results; therefore adjusted treatment effect estimates should be evaluated accordingly.

Table 21 Effect of Baseline and Post-baseline Covariates Gleason score 7-10 Prostate Cancer Diagnosis (Logistic Model) (Biopsied Population)

	Odds Ratio [a]	
	Estimate[b] (95% CI)	p-value
Baseline Covariates		
Treatment (dutasteride vs placebo)	0.92 (0.76, 1.12)	0.42
Time Period (Years 1-2, Years 3-4)	-	<0.0001
Age (yrs)	1.10 (1.08, 1.12)	<0.0001
Family History of Prostate Cancer	1.51 (1.16, 1.97)	0.0021
Baseline Prostate Volume (cc)	-	<0.0001
Baseline % Free PSA	-	<0.0001
Number of Cores at Entry Biopsy	0.95 (0.91, 0.99)	0.0119
Time Period * % Free PSA	-	<0.0001
Prostate Volume * % Free PSA	-	<0.0001
Baseline and Post-baseline Covariates		
Treatment (dutasteride vs placebo)	0.62 (0.49, 0.79)	0.0001
Time Period (Years 1-2, Years 3-4)	-	<0.0001
Age (yrs)	1.10 (1.07, 1.12)	<0.0001
Family History of Prostate Cancer	1.54 (1.15, 2.06)	0.0033
Baseline Prostate Volume (cc)	-	0.0003
Baseline % Free PSA	-	<0.0001
Number of Cores at Entry Biopsy	0.93 (0.89, 0.98)	0.0035
Time Period * % Free PSA	-	0.0016
Prostate Volume * % Free PSA	-	0.0004
Prostate Volume at Latest Biopsy (cc)	0.98 (0.97, 0.98)	<0.0001

a. Odds ratios are estimated using a logistic model containing the variables listed above and are adjusted for all other variables in the model.

b. Estimates are not provided for effects involved in interactions since these are not interpretable on an individual basis. Confidence intervals and p-values are computed using the Wald method.

3.2.1.3. Prostate Volume at Biopsy and Effect on High Grade Cancer Diagnosis

The majority of dutasteride subjects had lower prostate volumes at biopsy than the placebo group, however the incidence of Gleason score 7-10 cancers was lower in the dutasteride group than in the placebo group for subjects within the same prostate volume category (Table 22). This is the same as seen for all prostate cancers diagnosed, regardless of Gleason score (Table 15).

As seen for total prostate cancer diagnoses, the incidence of Gleason score 7-10 cancers generally decreased with increasing prostate volume. In both treatment groups, the incidence of high grade cancers (Gleason score 7-10) was greatest for subjects with prostate volumes of <30 cc (Table 22), whereas the majority of total prostate cancers diagnosed overall, were diagnosed in subjects with a prostate volume of <40 cc at biopsy (previously presented in Table 15). In the dutasteride group there was a higher incidence of Gleason 7-10 prostate cancer in the <20 cc category than in the 20 to <30 cc category (Table 22).

Within each prostate volume category, the incidence of high grade cancer diagnosis was lower in the dutasteride group than the placebo group, with the exception of 50 to <60cc where relatively no difference was seen.

Table 22 Gleason score 7-10 Prostate Cancer by Prostate Volume at Biopsy Overall (Biopsied Population)

Prostate Volume at Biopsy	Subjects[a] With Overall Gleason score 7- 10 Placebo N=3424 n/n[b] (%)	Dutasteride N=3305 n/n (%)
<20 cc	10/ 109 (9.2)	35/ 383 (9.1)
20 to <30 cc	46/ 431 (10.7)	56/ 966 (5.8)
30 to <40 cc	42/ 716 (5.9)	45/ 1061 (4.2)
40 to <50 cc	38/ 857 (4.4)	22/ 790 (2.8)
50 to <60 cc	17/ 777 (2.2)	11/ 465 (2.4)
60 to <70 cc	16/ 593(2.7)	4/ 266 (1.5)
70 to <80 cc	11/ 393 (2.8)	0/ 128
≥80 cc	12/ 543 (2.2)	0/ 107
Missing	41/ 648	47/ 566

a. Subjects with multiple biopsies may appear in multiple rows
b. Number of subjects with prostate volume

3.2.1.4. Proportion of High Grade Cancer By Prostate-Related Baseline Parameters

In the prostate cancer population, the proportion of high grade cancer (Gleason score 7-10) was evaluated by prostate cancer-related parameters at baseline (Table 23).

The proportion of Gleason score 7–10 prostate cancer was similar among testosterone and cancers within each treatment group. In both treatment groups, the proportion of cancers that were Gleason score 7–10 was increased as PSA increased and prostate volume decreased. There were higher ratios of Gleason score 7–10/total/cancers in the dutasteride group compared with the placebo group within each tertile (Table 23).

Table 23 Gleason score 7-10 Prostate Cancer at Post-baseline Biopsy by Baseline Prostate-Related Parameters (Prostate Cancer Population)

	Placebo N=858 n[a]/n[b] (%)	Dutasteride N=659 n[a]/n[b] (%)
PSA Tertiles (ng/mL)		
<5.1	72/ 281 (25.6)	68/ 223 (30.5)
5.1 to <6.8	73/ 281 (26.0)	66/ 210 (31.4)
≥6.8	87/ 287 (30.3)	85/ 223 (38.1)
Prostate Volume Tertiles (cc)		
<33.66	96/ 280 (34.3)	97/ 215 (45.1)
33.66 to <48.62	70/ 275 (25.5)	67/ 221 (30.3)
≥48.62	65/ 281 (23.1)	55/ 213 (25.8)
Testosterone Tertiles (nmol/L)		
<12.56	76/ 289 (26.3)	72/ 211 (34.1)
12.56 to <17.94	84/ 267 (31.5)	78/ 232 (33.6)
≥17.94	71/ 289 (24.6)	67/ 208 (32.2)
DHT Tertiles (nmol/L)		
<0.96	83/ 288 (28.8)	76/ 209 (36.4)
0.96 to <1.51	78/ 284 (27.5)	75/ 221 (33.9)
≥1.51	70/ 274 (25.5)	66/ 220 (30.0)

a. Subjects with Gleason score 7-10 prostate cancer
b. Number of Overall cancers

3.2.1.5. Summary of Gleason Score 8-10 Cancers

Baseline characteristics of subjects with no prostate cancer and with low grade cancers (Gleason score ≤6), and high grade cancers (Gleason score 7 cancers and Gleason score 8-10 cancers) are summarized in Appendix D Table 70. Compared to both no cancer and Gleason 2-6 cancers, Gleason 8-10 patients in both treatment groups tended to be slightly older, had a higher baseline PSA, a lower % free PSA, a lower prostate volume**,** and a higher PSA density at baseline.

When post-baseline prostate volume at the time of biopsy of Gleason score 7-10 cancers was added to the logistic regression analysis, the odds ratio of dutasteride compared with placebo for Gleason 7-10 cancers decreased from 0.92 (p=0.42) to 0.62 (p=0.0001) as described in Section 3.2.1.2. For the Gleason score 8-10 cancers, post-baseline prostate volume added to regression models resulted in lower treatment effect estimates for both the logistic and log-binomial regression models: the treatment odds ratio decreased from 1.48 (p=0.18) to 1.08 (p=0. 83) for the logistic, treatment relative risk went from 1.47 (p=0.19) to 1.08 (p=0.83) for the log-binomial. Again, this highlights the effect and relevance of prostate volume at biopsy on the likelihood of high grade prostate cancer diagnoses, as reported in the literature [Kulkarni, 2006]. As previously noted, use of post-baseline covariates in regression models can result in difficulties in interpretation of results; therefore adjusted treatment effect estimates should be evaluated accordingly.

Individual subject data for those subjects with Gleason score 8-10 cancers are presented in Appendix D Table 71.

3.2.1.6. For-Cause Biopsies and Gleason Scores

In REDUCE, there were fewer for-cause biopsies as well as fewer cancers diagnosed in the dutasteride group compared with the placebo group (placebo: 86 cancers from 850 needle biopsies, 2.1% of Efficacy population; dutasteride: 63 cancers from 657 needle biopsies, 1.6% of Efficacy population). The distribution of the Overall Gleason scores for the subjects with prostate cancer initially detected via for-cause biopsies indicated that there were lower number of Gleason 6 in the dutasteride group, similar numbers of Gleason score 7 and 8 cancers in both treatment groups with more Gleason score 9 and 10 cancers in the dutasteride group (Table 24).

Table 24 Overall Gleason Scores from For-Cause Biopsies in REDUCE

	Number of Subjects	
	Placebo N=86[a]	Dutasteride N=63[a]
Overall Gleason score[b]	n (%)	n (%)
5	0	1 (1.6)
6	56 (65.1)	27 (42.9)
7	26 (30.2)	27 (42.9)
8	3 (3.5)	3 (4.8)
9	1 (1.2)	4 (6.3)
10	0	1 (1.6)

a. Subjects with procedure type "U," unscheduled include protocol-independent and protocol-dependent biopsies (outside and inside, respectively, of date range for Year 2 and Year 4 biopses).
b. Overall Gleason score = score at initial diagnosis of PCa

The differences in within group Gleason score distribution (56% Gleason score 7-10 in dutasteride vs. 35% in placebo) could be explained by the improved ability of final PSA and PSA changes from month 6 of treatment to final PSA to detect high grade tumors in subject treated with dutasteride compared with placebo discussed in Section 3.2.2.2. Given that 80% of dutasteride for-cause biopsies (87% in placebo) were driven by rises in PSA over time, it could be expected that the increased sensitivity in PSA associated with dutasteride when using final PSA or change from month 6 PSA, would result in increased detection of higher grade disease.

3.2.1.7. Dutasteride Effects on Prostate Cancers

Prostate cancer growth and progression are not well understood, in part because of the imprecise nature of prostate biopsies. A high grade cancer detected during REDUCE may have been an pre-existing high grade cancer not detected on prior biopsies, may have developed *de novo*, or may have developed from a previously undetected low grade cancer.

Given what is understood about prostate biopsy and grading, and about the heterogeneity of prostate tumors, there are several possible explanations for the observed differences in

the number of high grade Gleason score 8-10 cancers between the dutasteride and placebo groups in Years 3-4 of the REDUCE study.

Dutasteride may induce growth of some high-grade cancers in this patient population. Although this study was not powered nor designed to evaluate the impact of dutasteride on high grade tumors, the possibility that some high grade cancers may be induced by treatment cannot be definitively refuted based on available data. However, this seems unlikely in view of other potential explanations for the differences in the number of Gleason 8-10 tumors between dutasteride and placebo, including data from other randomized clinical trials.

Dutasteride preferentially suppresses low grade cancer resulting in a higher likelihood of detecting high grade cancers. The detection of prostate cancer on biopsy is subject to the ratio of tumor volume to prostate volume [Crawford, 1998; Mariappan, 2004]. The grading of prostate cancer on biopsy is subject to the relative proportions of Gleason patterns within the tumor foci. The greater the relative volume of any high grade component, the more likely the high grade component will be detected [Lucia, 2007]. As prostate cancer is a multifocal and heterogenous disease with the potential of different cancers existing at the same time, it is possible that dutasteride treatment results in a *selective inhibition of low grade cancers* in men whose prostates contain both low- and high grade cancers. Such inhibition could *enhance the relative proportion of high to low grade cancers* such that the high grade tumors would be more likely detected by needle biopsy [Lucia, 2007]. Smaller high grade tumors that were missed in a previous biopsy might be detected at a later biopsy.

Dutasteride reduces prostate volume making high grade tumors more easily detected. Prostate cancer is easier to detect in smaller prostate glands [Basillote, 2003; Kulkarni, 2006]. In REDUCE the number and location of biopsy cores was standardized, but the biopsy schema was not adjusted for prostate volume and hence, the likelihood of diagnosing prostate cancer would be increased in smaller prostates, assuming no change in tumor volume. At Year 2 biopsies, the mean prostate volume in the dutasteride group decreased by 17.4% compared with a mean increase in the placebo group of 13%. At Year 4 biopsies, the mean prostate volume in the dutasteride group decreased by 17.5% compared with a mean increase of 19.7% in the placebo group (Table 14)

In a mathematical model of prostate cancer detection on biopsy, it was estimated that there would be an increase in tumor detection of 11 to17% with dutasteride, assuming a 25% reduction in prostate volume and no decrease in tumor volume [Serfling, 2007]. The difference in prostate volume between the placebo and dutasteride groups is greater than 25%. Prostate volume reduction could explain only part of the difference in the number of subjects with high grade tumors between the dutasteride and placebo groups in Years 3-4 since most of the difference in prostate volume between the treatment groups occurred during the first two years However, while the mean adjusted prostate volume in the dutasteride group did not change from Year 2 to Year 4, prostate volume increased in the placebo group exaggerating the prostate size difference between the treatment groups at the Year 4 biopsies. This could possibly make it less likely for biopsy to identify high grade cancer components in these larger placebo-treated prostates, especially if a low grade component was not selectively inhibited.

Enhanced biopsy sensitivity to detect high grade tumors. Biopsies have the inherent limitations of being comprised of small histological samples, with the potential for misclassification of the patient's true Gleason score since these biopsies are only partially representative of the entire prostate and there are often a variety of tumor types coexisting in the prostate. Pathological analysis of prostate samples from subjects undergoing radical prostatectomy demonstrated an *enhanced sensitivity of biopsy for detection of high grade cancer* in the group treated with finasteride compared with placebo in the PCPT trial [Lucia, 2007]. Consistent with these findings, of the subjects in REDUCE who had surgical procedures after biopsies, a larger proportion of dutasteride subjects had biopsy Gleason scores confirmed at surgery compared with placebo subjects (58.6% of dutasteride-treated subjects versus 50% of placebo subjects). Although the sample size was small and the processing of histological samples submitted by local laboratories were not standardized, these data are consistent with available literature and lend support to a more accurate and reliable grading of cancers in patients under 5ARI treatment.

Study design bias introduced in Years 3-4. In REDUCE, the population of subjects biopsied in Year 2 represented a truly randomized population. Because more men in the placebo group were removed from the study during the first two years due to the diagnosis of prostate cancers, the treatment groups biopsied in Years 3-4 no longer represented a strictly randomized population. During Years 1-2, the number and percentage of high grade cancers did not differ between the treatment groups. However, 141 more subjects in the placebo group than in the dutasteride group were diagnosed with Gleason score 5-7 cancers at the Year 2 biopsy and were removed from the study. Should those 141 subjects have continued in the study and been rebiopsied at Year 4, some of them may have been reclassified with a higher Gleason score cancer. If, for example, 3%, 5% or 8% of these excess 141subjects remained in the study, there would be 4, 7 or 11 additional high grade Gleason 8-10 tumors, respectively, in the placebo group at Year 4 biopsy. Although this is a hypothesis that cannot be tested in this study, rebiopsy of such men undergoing active surveillance indicated that 8% of the men with a Gleason score 4-7 would be found to harbor Gleason 8-10 tumor components that were not identified on the initial biopsy in a subsequent biopsy at a median of 22 months [Choo, 2007].

The *results of other randomized trials of dutasteride* do not suggest that dutasteride increases high grade tumors. The durations of these trials were shorter or equal to dutasteride. In CombAT, a 4-year randomized BPH study comparing dutasteride and tamsulosin combination therapy with the individual monotherapies, all biopsies were for-cause, and prostate cancer was captured as an adverse event (Section 3.3). The incidence of prostate cancer was 40% lower in the two dutasteride arms combined compared to the tamsulosin monotherapy arm, and the reduction was consistent across all Gleason score categories. Although CombAT was not designed to evaluate prostate cancer endpoints, if dutasteride stimulated the growth of high grade prostate cancers, one would have expected this to result in a greater number of high grade cancers in the dutasteride arms in Years 3-4 of CombAT.

In REDEEM, a 3-year randomized study comparing dutasteride with placebo treatment of male subjects diagnosed with low-risk, localized prostate cancer (Gleason score ≤6) who were candidates for or undergoing expectant management, there were similar numbers of

upgrading to Gleason 7 and 8 cancers on subsequent biopsy in the two study arms (Section 5.4.2). In addition, there were no subjects with Gleason 9-10 cancers diagnosed in either treatment group on final biopsy. Similar to the REDUCE study, biopsies in REDEEM were planned, in this case, at 18 months and 3 years of treatment. Subjects were discontinued from study medication if they experienced pathological or therapeutic progression. At the 18 month biopsy, there were 2 Gleason score 8-10 cancers in the placebo group and none in the dutasteride group. At the 3 year biopsy there were 3 Gleason score 8 cancers in the placebo group and 2 cancers in the dutasteride group.

In addition to the review of data from the studies described here, there is also no basic scientific evidence that dutasteride stimulates the growth of high grade cancers. In animal models, dutasteride inhibits prostate cancer cell growth. The best example of this is the research demonstrating that dutasteride was the only 5ARI to inhibit growth of Dunning tumor xenografts in rats, and that this growth reduction required inhibition of both 5α-reductase isoenzymes [Xu, 2006]. Similar effects of dutasteride have been shown in explants of human prostate cancers where dutasteride reduced cell growth in 78% of cancers, whereas finasteride was effective in 39% [Festuccia, 2008]

There is no evidence that a low DHT level, similar to the action of dutasteride, is associated with a higher risk of prostate cancer or high grade tumors. A meta-analysis performed across 18 studies, involving over 10,000 men found no significant relationship between testosterone, free testosterone, and DHT and the risk of prostate cancer overall, advanced prostate cancer or high grade prostate cancer. There was a trend towards lower serum DHT levels being associated with a higher incidence of localized prostate cancer, but the opposite was true for advanced prostate cancer [Roddam, 2008]. In REDUCE, there was no association between baseline serum testosterone or DHT and the eventual detection of either prostate cancer overall or high grade prostate cancer.

In summary, the explanation of the findings of a difference between the dutasteride and placebo treatment groups in the number of high grade tumors at Years 3-4 biopsies is likely due to a combination of factors. The possibility that dutasteride could in some cases induce high grade tumors can not be definitively excluded, although the lack of an increase in CombAT and REDEEM make this less likely.

3.2.2. PSA and Prostate Cancer Analyses

PSA diagnostic performance and dutasteride's effect were evaluated in different ways in the REDUCE trial. The analyses defined in the Reporting and Analysis Plan to investigate the relationship between PSA values and prostate cancer diagnosis used both final post-baseline PSA, and PSA change from nadir to final PSA as PSA measures, and both prostate cancer occurrence and occurrence of Gleason score 7-10 as endpoints.

In routine clinical practice, rather than considering single PSA values, physicians usually follow PSA values over time to make diagnostic and treatment decisions, with monitoring intervals depending on PSA values and perceived prostate cancer risk level [National Comprehensive Cancer Network, 2010]. Thus, post-hoc area under the curve (AUC) and Receiver Operating Characteristics (ROC) post-hoc analyses were conducted on additional PSA measures and endpoints to further evaluate dutasteride's effect in a

similar way to current clinical practice. These additional PSA analyses included: change from Month 6 to final PSA, change from Month 12 to final PSA, and change from Month 18 to final PSA for overall prostate cancers, Gleason 7-10 cancer diagnoses, cancers with four or more positive biopsy cores, and cancers meeting the Epstein Criteria for pathological insignificance (no core with more than 50% involvement of cancer, Gleason score <7, fewer than 3 cores involved, PSA density <=0.15ng/mL per g). The definition for Epstein criteria was modified to exclude PSA density, as prostate volumes were missing for some subjects. In addition, only PSA values prior to the latest post-baseline biopsy were included in the analyses so as to temporally align the relevant assessments.

There are several limitations to these analyses and translation of results to clinical practice should be approached with caution. PSA values on or within 42 days after a biopsy were omitted from the analyses in order to avoid the known effect of biopsies to increase PSA values. PSA evaluations were conducted at fixed 6 month intervals and abnormal values of PSA were not confirmed by repeat testing. In fact, when assessing change from nadir, it became apparent that the chance of a spurious PSA value defining a nadir was increased, if the lowest of all 9 potential PSA (baseline and every 6 months determination for 4 years) values was used for a given subject. Rather than try to develop an algorithm to censor spurious PSA values, Month 6 was defined as the nadir for the purposes of assessing subsequent PSA changes (dutasteride reduces PSA by approximately 50% at month 6)

However, the analyses of changes in PSA after 6 months of treatment, also have limitations. There were cases where subjects' PSA decreased further after the 6 month evaluation before it started to increase, but the increase did not exceed the threshold of the Month 6 PSA. While in clinical practice this increase in PSA may have caught the attention of the physician, these subjects are not counted in the calculations of PSA increases from Month 6 PSA and are considered in the analysis as undetected cancers (Table 27). There were other subjects who had a PSA rise exceeding the Month 6 PSA threshold but were not included in these analyses as their increased PSA value was taken within 42 days of the date of biopsy.

3.2.2.1. PSA changes during the first 6 months of treatment and Prostate Cancer Diagnosis

During the initial 6 months of dutasteride treatment, there was no significant difference in the PSA suppression in men who did or who did not develop biopsy-detectable prostate cancer during the study. This initial decrease was also similar between subjects without cancer and those who developed Gleason score 7-10 cancers. This lack of discrimination was not only true for mean values, but also for the extremes of PSA suppression (Table 25). This lack of discrimination may be due to the ability of dutasteride to suppress PSA from any prostate tissue.

Table 25 PSA Percent Change from Baseline to Month 6 (Biopsied Population, LOCF)

	PSA Percent Change from Baseline to Month 6 (%)					
	No prostate cancer diagnosis		Gleason score 5–6		Gleason score 7–10	
Change	Placebo N=2566	Dutasteride N=2646	Placebo N=617	Dutasteride N=437	Placebo N=233	Dutasteride N=220
10th percentile	-37.68	-69.57	-36.17	-67.92	-22.22	-70.42
25th percentile	-22.45	-61.22	-20.00	-58.33	-7.07	-60.00
50th percentile	-5.66	-50.00	-3.39	-50.00	3.24	-49.15
75th percentile	11.29	-37.88	13.73	-38.36	20.81	-35.14
90th percentile	30.14	-22.50	28.57	-22.73	41.76	-18.75

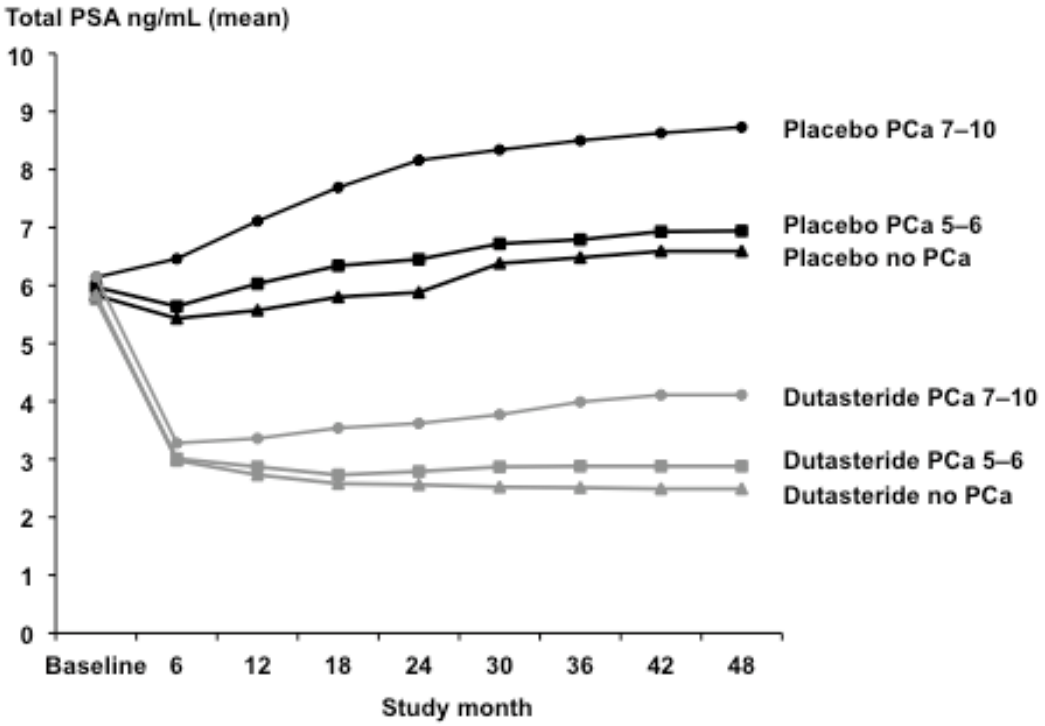
LOCF=last observation carried forward

3.2.2.2. PSA changes after the first 6 months of treatment and Prostate Cancer Diagnosis

When observing PSA changes over time there were differences between the treatment groups. In the placebo group, PSA tended to increase irrespective of the subjects' underlying prostate cancer status; the rise in PSA for these subjects was greatest in men with Gleason 7-10 cancers. In the dutasteride arm, after the initial expected decline, PSA values in men with cancer (Gleason 7-10) tended to rise, whereas PSA values in men with low-grade (Gleason ≤6) or no cancer tended to decrease or remain stable (Figure 3).

The majority of dutasteride-treated subjects did not experience an increase in PSA values after Month 6, whereas the majority of placebo-treated subjects did so regardless of cancer status. If this approach to PSA use was translated into clinical practice this could result in lower opportunities for false PSA signals to trigger a biopsy in those dutasteride-treated subjects, thus reducing the overall number of biopsies. This has been observed in subjects with for-cause biopsies in REDUCE (Section 3.2.1.6) and in CombAT (Section 3.3 and Table 37).

Figure 3 **Mean PSA by prostate cancer status (no cancer, Gleason score 5–6 cancer, and Gleason score 7–10 cancer) for the dutasteride and placebo groups over the course of the study (Biopsied Population)**



3.2.2.3. AUC of ROC for Final Post-Baseline PSA, PSA Changes from Nadir, and PSA Changes from Month 6 for Gleason Score 7-10 Cancers

The AUC of the ROC curves using final PSA at Year 4 and changes form Month 6 to final PSA for Gleason score 7-10 cancers were significantly higher for dutasteride compared with placebo group (Table 26). The increase in change from nadir was not significantly different.

Table 26 Area Under the Receiver Operating Curve Values for Prostate Cancer Diagnosis (Gleason Score 7-10 Cancer) Using PSA Parameters in REDUCE (Biopsied Population)

PSA Parameter	AUC of ROC (SE)		
	Dutasteride (0.5 mg) (n=3305)	Placebo (n=3424)	p-value
Final PSA	0.700 (0.019)	0.650 (0.018)	0.0491
Change in PSA from Month 6 to final PSA	0.699 (0.019)	0.593 (0.019)	0.0001
Change from Nadir to Final PSA	0.633 (0.021)	0.603 (0.019)	0.29

Table 27 illustrates how prostate cancer characteristics change by treatment group as the PSA changes from Month 6 to final PSA increase. In both treatment groups, there were men who were diagnosed with prostate cancer without an associated rise in PSA: 23.5% in placebo (222/944), 15.6 % in dutasteride (363/2330). Likewise a similar percentage of subjects with Gleason score 7- 10 cancers in each treatment arm did not have a PSA increase after month 6: 4.6 % in placebo(43/936), 4% in dutasteride (93/2328).

If only those men with an increase from month 6 PSA to final PSA were biopsied, 43 of 229 (19%) of Gleason score 7–10 cancers would not have been detected in the placebo group, and 93 of 217 (43%) such cancers would not have been detected in the dutasteride group. Of those, 21% and 26% of men in the placebo and dutasteride groups, respectively, would be Gleason score 4+3 or higher.

Table 27 Incidence of All Prostate Cancers, Gleason Score 7-10 Cancers, Gleason Score 3+4 Cancers, and Cancer Volumes by PSA Changes from Month 6 to Final PSA (Biopsied Population)

	Change in Month 6 to final PSA (ng/mL)				
	No increase	Increase of 0.1–1.0	Increase of 1.1–2.0	Increase of >2.0	Any increase
	Dutasteride group				
Overall incidence of prostate cancer	15.6% (363/2330)	29.1% (172/591)	31.5% (46/146)	34.3% (69/201)	30.6% (287/938)
Incidence of Gleason score 7–10 prostate cancer	4.0% (93/2328)	10.3% (61/590)	14.5% (21/145)	20.9% (42/201)	13.2% (124/936)
Percent of cancers that are Gleason score 7–10	25.6% (93/363)	35.5% (61/172)	45.6% (21/46)	60.9% (42/69)	43.2% (124/287)
Percent of Gleason score 7–10 cancers that are Gleason score 3+4	74.2% (69/93)	68.9% (42/61)	61.9% (13/21)	52.4% (22/42)	62.1% (77/124)
Percent of cancers meeting Epstein Criteria for pathological insignificance[a]	67.6% (244/361)	56.4% (97/172)	52.2% (24/46)	29.4% (20/68)	49.3% (141/286)
Mean volume of Gleason score 7–10 prostate cancer on biopsy (ccx10^{-3})	3.4	4.1	4.1	6.2	4.8
	Placebo group				
Overall incidence of prostate cancer	23.5% (222/944)	24.1% (191/793)	25.1% (160/637)	27.3% (274/1003)	25.7% (625/2433)
Incidence of Gleason score 7–10 prostate cancer	4.6% (43/936)	5.4% (43/789)	7.1% (45/636)	9.8% (98/1003)	7.7% (186/2428)
Percent of cancers that are Gleason score 7–10	19.4% (43/222)	22.5% (43/191)	28.1% (45/160)	35.8% (98/274)	29.8% (186/625)
Percent of Gleason score 7–10 cancers that are Gleason score 3+4	79.1% (34/43)	81.4% (35/43)	75.6% (34/45)	71.4% (70/98)	74.7% (139/186)
Percent of cancers meeting Epstein Criteria for pathological insignificance[a]	68.2% (150/220)	66.0% (124/188)	60.4% (96/159)	53.1% (144/271)	58.9% (364/618)
Mean volume of Gleason score 7–10 prostate cancer on biopsy (cc x10^{-3})	3.8	2.8	5.5	6.0	5.1

Epstein criteria involve the following: no core with more than 50% involvement of cancer, Gleason score <7, fewer than 3 cores involved, PSA density <=0.15ng/mL per g (using PSA values within 7 days of diagnosis). The definition for Epstein criteria was modified to exclude PSA density, as corresponding values were missing for some subjects.

Interpreting these results, however, should be approached with caution as the clinical study setting does not reproduce usual clinical practice and there are associated limitations (Section 3.2.2).

Current guidelines would not recommend, for instance, to biopsy a man who has any increase in his PSA without considering the magnitude of that increase. If the NCCN criteria for biopsy is applied to the placebo subjects in REDUCE (e.g., monitoring the velocity of PSA changes per year, i.e., for PSA >2.5 -4 PSA velocity≥0.35ng/mL/yr and for PSA 4 -10 ng/mL, PSAVelocity≥0.75 ng/mL/yr [National Comprehensive Cancer Network, 2010], the number of undetected Gleason score 7-10 cancers would be 82. This

is similar to the 93 missed Gleason score 7-10 cancers in the dutasteride group using PSA changes (increases) from Month 6. (Appendix D Table 72)

If the current dutasteride label recommendations for monitoring PSA were applied for dutasteride subjects, i.e., evaluation of those patients with PSA increases from their nadir PSA, the number of potentially missed Gleason score 7-10 cancers will then be 54.(Appendix D Table 73)

When using appropriate comparisons to estimate the potential Gleason score 7-10 cancers that could be missed if PSA monitoring guidelines were followed, the numbers in the dutasteride group are either similar to placebo (93 vs. 82 missed cancers, respectively) or lower than placebo (54 vs 82 undetected cancers, respectively).

Gleason 8-10 cancers

Nine (9) Gleason score 8-10 cancers in the dutasteride group vs. 4 in the placebo group would have been missed using increases from Month 6 PSA to final PSA as the criteria for biopsy. If the current label recommendations for dutasteride biopsy are applied (i.e., changes from nadir) and NCCN guidelines based on PSA velocity are applied for placebo, 22/29 (76%) of dutasteride and 14/19 (74%) of placebo Gleason score 8-10 cancers would have been detected. Alternatively 7/29 (24%) dutasteride and 5/19 (26%) placebo Gleason score 8-10 cancers would not have been detected.

Of note, among a subset of subjects in the dutasteride group with Gleason score 8-10 cancers and at least 3 post-baseline measurements during Years 1-2, 16 subjects were identified. Ten of these cancers occurred in subjects with a rise in PSA from nadir. Four of the 16 also had rises from nadir, but these occurred on the date of the biopsy which excluded them from analysis. The mean tumor volume on biopsy of these 10 tumors was 5.26 ± 2.99 cc $x10^{-3}$ compared with 1.38 ± 1.34 cc $x10^{-3}$ in the six Gleason score 8–10 tumors without a PSA rise (volume measured in cc $x10^{-3}$, determined by the linear extent of the tumor multiplied by the biopsy cross-sectional area). During Years 3–4, there were 12 Gleason score 8–10 tumors in the dutasteride arm and all were associated with a rise in PSA from nadir. Their mean tumor volume was 7.62 ± 5.71 cc $x10^{-3}$.

Individual subject data for those subjects with Gleason Score 8-10 cancers are presented in Appendix D Table 71.

In summary, dutasteride treatment does not interfere with the predictive value of PSA to detect overall prostate cancer and high grade prostate cancer.

3.2.3. Pathological Characteristics

3.2.3.1. Amount of Prostate Cancer on Biopsy

Among the subjects with biopsy-detectable prostate cancer the two treatment groups were similar with respect to the mean number of positive cores (1.8 in the dutasteride group and 1.9 in the placebo group), percentage of cores with cancer (12.2% and 13.4%, respectively) and tumor volume (0.0022 mL and 0.0024 mL, respectively).

3.2.3.2. HGPIN and ASAP

The diagnosis of HGPIN and ASAP increases the likelihood of a future diagnosis of prostate cancer, and as such, they may be either precursor lesions for prostate cancer (HGPIN) or lesions predictive of future Prostate cancer (ASAP) [Bostwick, 2006; Montironi, 2006]. Patients with HGPIN and/or ASAP are closely monitored with repeated prostate biopsies being a common approach.

Dutasteride significantly reduced both HGPIN and ASAP (Table 28). The expected clinical translation would be a lower number of dutasteride patients undergoing repeat biopsies, thus reducing the burden on patients and health care systems that would result from these procedures and their potential complications. It also reflects that dutasteride may affect earlier stages of cancer and this impact might be seen years later than the impact seen on lower Gleason score tumors.

In the efficacy population there was a lower incidence of HGPIN and/or ASAP with or without associated prostate cancer in the dutasteride group compared with placebo (10% dutasteride vs. 17% placebo). The incidence of HGPIN and/or ASAP without the presence of prostate cancer was lower in the dutasteride group than placebo group (6% dutasteride vs. 9% placebo, $p<0.0001$[Table 28]).

In the efficacy population the incidence of HGPIN without the presence of prostate cancer and the incidence of ASAP without the presence of prostate cancer was lower in the dutasteride group than in the placebo group (4% dutasteride vs. 7% placebo for HGPIN, $p<0.0001$ and 3% dutasteride vs. 4% placebo for ASAP, $p=0.0205$ [Table 28]). The relative risk reduction of HGPIN without the presence of prostate cancer was 43.3% ($p<0.0001$) for dutasteride compared with placebo and for ASAP without the presence of prostate cancer was 23.5% ($p=0.0205$) for dutasteride compared with placebo.

Table 28 Number of Subjects with HGPIN, ASAP and/or Biopsy-Detectable Prostate Cancer at Post-baseline Biopsy in REDUCE (Efficacy Population)

Time Period	Placebo N=4073 n/N[a](%)		Dutasteride N=4049 n/N[a] (%)
HGPIN and no Prostate cancer			
Years 1-2	161 (4)		81 (2)
Years 3-4	153 (4)		100 (2)
Overall	268 (7)		151 (4)
Overall p-value[b]		<0.0001	
HGPIN and No ASAP and no Prostate cancer			
Years 1-2	123 (3)		65 (2)
Years 3-4	124 (3)		83 (2)
Overall	206 (5)		121 (3)
Overall p-value[b]		<0.0001	
ASAP and no Prostate cancer			
Years 1-2	118 (3)		102 (3)
Years 3-4	97 (2)		62 (2)
Overall	167 (4)		127 (3)
Overall p-value[b]		0.0205	
HGPIN and/or ASAP			
Years 1-2	418 (10)		255 (6)
Years 3-4	318 (8)		196 (5)
Overall	675 (17)		409 (10)
HGPIN and/or ASAP and no Prostate Cancer			
Years 1-2	241 (6)		167 (4)
Years 3-4	221 (5)		145 (4)
Overall	373 (9)		248 (6)
Overall p-value[b]		<0.0001	
HGPIN, ASAP, and/or Prostate Cancer Diagnosis			
Years 1-2	819 (20)		602 (15)
Years 3-4	501 (12)		369 (9)
Overall	1231 (30)		907 (22)
Overall p-value[b]		<0.0001	

a. n=number of subjects with diagnosis
b. p-value vs. Placebo based on Fisher's exact test.

For subjects in the biopsied population with HGPIN or ASAP who were subsequently diagnosed with prostate cancer, the incidence of prostate cancer was lower in the dutasteride group than the placebo group (26% dutasteride vs. 28% placebo).

The mean volume of HGPIN for Years 1-2 biopsies and overall post-baseline biopsy was lower in the dutasteride group (0.0259 and 0.0446 cc $x10^{-3}$, respectively) than placebo group (0.0658 and 0.1105 cc $x10^{-3}$, respectively) irrespective of whether prostate cancer was subsequently confirmed ($p<0.0001$, statistically significant for both).

3.2.3.3. Post-Biopsy Events

Overall, the incidence of post-biopsy events which occurred within 7 days after the biopsy was lower in the dutasteride group than the placebo group (4.4% vs. 7.3%, $p<0.0001$). The incidence of UTIs was lower in the dutasteride group than the placebo

group (0.3% vs. 0.9%, p=0.0017). There was a trend for the reduction of incidence of post-biopsy hematuria and hematospermia compared with placebo as the reduction with both endpoints was nominally significant (p<0.05 [Table 29]).

Table 29 Post-Biopsy Hematuria, Hematospermia and UTI (Efficacy Population)

Post-Biopsy Events		Placebo N=4073		Dutasteride N=4049
Any Post-Biopsy Event	n (%) (95% CI) p-value	297 (7.3) (6.5, 8.1)	<0.0001	180 (4.4) (3.8, 5.1)
Macroscopic Hematuria	n (%) (95% CI) p-value	168 (4.1) (3.5, 4.7)	0.0177	127 (3.1) (2.6, 3.7)
Macroscopic Hematospermia	n (%) (95% CI) p-value	78 (1.9) (1.5, 2.3)	0.0342	53 (1.3) (1.0, 1.7)
UTI	n (%) (95% CI) p-value	37 (0.9) (0.6, 1.2)	0.0017	14 (0.3) (0.2, 0.5)
Duration of UTI (Days)	N Mean (SD)	35 11.9 (6.83)		13 15.5 (18.04)
Duration of Macroscopic Hematuria (days)	N Mean (SD)	157 11.2 (30.83)		122 15.8 (65.80)
Duration of Macroscopic Hematospermia (days)	N Mean (SD)	65 29.3 (43.9)		45 13.8 (13.11)

3.2.4. Stage of Cancer

Overall in both treatment groups, most of the prostate cancers diagnosed were in the early stages, with TNM tumor classification of T1 or T2 (94.4% in the dutasteride group and 93.2% in the placebo group). As expected with early stage prostate cancer, there were only a few subjects in each treatment group with positive nodes (N1 or N2) or with metastases (M1A, B, or C). There was no evidence of more advanced cancer in either treatment group. In both groups, however there was a high incidence of subjects where nodal status and metastases status (NX and MX) was not assessed (Table 30).

Table 30 Summary of Initial and Latest TNM Stages for Subjects with Biopsy-Detectable Prostate Cancer (Biopsied Population)

		Placebo N=3424 n (%)		Dutasteride N=3305 n (%)	
Stage		Initial Stage	Latest Stage	Initial Stage	Latest Stage
T1 or T2	n	442	439	304	303
	Yes	415 (93.9)	409 (93.2)	290 (95.4)	286 (94.4)
	No	27 (6.1)	30 (6.8)	14 (4.6)	17 (5.6)
N Stage	n	441	442	304	303
	N0	235 (53.3)	253 (57.2)	158 (52.0)	166 (54.8)
	N1	6 (1.4)	6 (1.4)	1 (0.3)	2 (0.7)
	N2	1 (0.2)	1 (0.2)	0	0
	NX	199 (45.1)	182 (41.2)	145 (47.7)	135 (44.6)
M Stage	n	440	441	304	303
	M0	236 (53.6)	246 (55.8)	176 (57.9)	178 (58.7)
	M1A	0	1 (0.2)	1 (0.3)	0
	M1B	1 (0.2)	1 (0.2)	1 (0.3)	2 (0.7)
	M1C	1 (0.2)	1 (0.2)	0	0
	MX	202 (45.9)	192 (43.5)	126 (41.4)	123 (40.6)

3.2.5. Death and Survival

REDUCE was not designed to make any evaluation on the impact of dutasteride on mortality. No deaths due to prostate cancer were reported during the study. The overall survival rate was similar for both treatment groups (77 deaths in the placebo group and 70 in the dutasteride group). The most frequent cause of death in both treatment groups was myocardial infarction (13 subjects in the placebo group compared with 7 subjects in the dutasteride group). Deaths are discussed in further detail in Section 7.6.1.

3.2.6. Intervention for Treatment of Prostate Cancer

3.2.6.1. Surgical and Non-Surgical Interventions

Over 90% of the surgical and non-surgical interventions were the results of diagnoses during Years 1-2 resulting in treatments during Years 3-4. Subject follow-up data were collected until 4 months after the Year 4 assessment such that intervention data may not have been obtained for patients diagnosed with PCa at Year 4.

Dutasteride treatment significantly reduced the risk of intervention for the treatment of prostate cancer ($p<0.0001$). In the placebo and dutasteride groups, 10.8% and 7.4%, respectively, of all subjects in the Efficacy population, underwent any intervention for prostate cancer. In both treatment groups, more subjects had surgical treatment than non-surgical treatment. The most commonly used non-surgical treatment was external beam radiotherapy (Table 31).

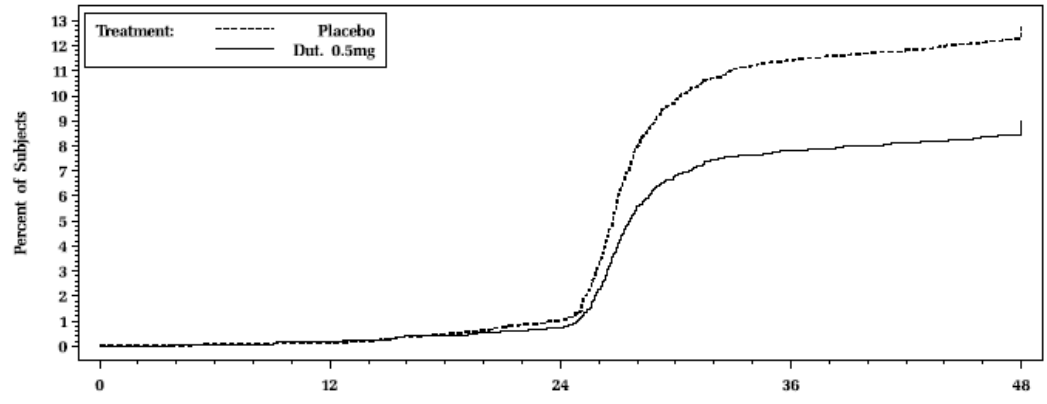
Table 31 Summary of Surgical and Non-Surgical Intervention for Prostate Cancer (Efficacy Population)

Reason for, and type of intervention for Prostate Cancer	Time Period[a]	Placebo N=4073 n (%)	Dutasteride N=4049 n (%)
Any Intervention	Years 1 - 2	37 (0.9)	27 (0.7)
	Years 3 - 4	401 (11)	273 (8)
	Overall	438(10.8)	300 (7.4)
	p-value	<0.0001	
Any surgical Intervention	Years 1 - 2	25 (<1)	22 (<1)
	Years 3 - 4	280 (7)	199 (5)
	Overall[b]	304 (7)	221 (5)
Any non-surgical intervention	Years 1 - 2	16 (<1)	7 (<1)
	Years 3 - 4	157 (4)	89 (2)
	Overall	172 (4)	95 (2)
Drug therapy	Years 1 - 2	8 (<1)	6 (<1)
	Years 3 - 4	77 (2)	50 (1)
	Overall	84 (2)	55 (1)
External Beam Radiation therapy	Years 1 - 2	6 (<1)	2 (<1)
	Years 3 - 4	101 (2)	55 (1)
	Overall	107 (3)	57 (1)
Other	Years 1 - 2	3 (<1)	1 (<1)
	Years 3 - 4	16 (<1)	12 (<1)
	Overall	19 (<1)	13 (<1)

a. Most interventions in Years 3-4 were the result of diagnoses during Years 1-2.
b. Brachytherapy was included in the surgical intervention category (20 subjects in the placebo group and 14 subjects in the dutasteride group)

The time to prostate cancer intervention was similar between treatment groups until Years 3-4, with a lower occurrence of treatment intervention in the dutasteride group compared with placebo (Figure 4). Most prostate cancers were diagnosed from protocol-dependent biopsies at Year 2 and Year 4. However; as noted above, treatments that occurred during Years 3-4 were primarily in response to prostate cancers diagnosed during Years 1-2.

Figure 4 Kaplan-Meier Estimates of Time to Intervention for Prostate Cancer (Efficacy Population)



Placebo Group				
Cumulative no. of events	6	37	395	438
No. at risk	4073	3816	3524	2850
Dut. 0.5mg Group				
Cumulative no. of events	7	27	265	300
No. at risk	4049	3734	3424	2908

3.2.6.2. Hospitalizations

The number of total cumulative days (TCD) of hospitalization for prostate cancer surgeries and prostate-related surgeries was lower in the dutasteride group than in the placebo group. In general, TCD of hospitalization was also lower in the dutasteride group than placebo group, with the exception of hospitalization due to drug therapy, external beam radiation and macroscopic hematuria (Table 32).

Table 32 Hospitalization for Prostate-Related Interventions and Events (Efficacy Population)

Reason for Hospitalization		Placebo N=4073	Dutasteride N=4049
Prostate Cancer-Related Surgery	N	267	199
	Mean Days	7.5	7.4
	Total Cumulative Days[a] (TCD)	2002.5	1472.6
Total Prostate Surgeries (any reason)	N	429	248
	Mean Days	7.3	7.1
	TCD[a]	3131.7	1760.8
Prostate Cancer Drug Therapy Intervention	N	1	3
	Mean Days	8.0	19.7
	TCD[a]	8.0	59.1
External Beam Radiation Therapy	N	2	4
	Mean Days	8.0	21.8
	TCD[a]	16.0	87.2
Prostate Cancer Other Non-surgical Therapy	N	5	6
	Mean Days	6.4	2.0
	TCD[a]	32	12
Total Prostate Related Hospitalization (Surgical or Non-surgical)	N	435	255
	Mean Days	7.3	7.2
	TCD[a]	3175.5	1836
BPH-Related Surgery	N	177	51
	Mean Days	6.8	5.9
	TCD[a]	1203.6	300.9
AUR	N	81	28
	Mean Days	5.8	6.1
	TCD[a]	469.8	170.8
UTI	N	38	19
	Mean Days	6.7	7.7
	TCD[a]	254.6	146.3
Macroscopic Hematuria	N	6	7
	Mean Days	3.7	3.4
	TCD[a]	22.2	23.8
Macroscopic Hematospermia	N	2	0
	Mean Days	2.0	
	TCD[a]	4.0	
Other-related Surgery	N	17	12
	Mean Days	7.8	7.1
	TCD[a]	132.6	85.2

a. Cumulative days derived by multiplying n x mean days.

3.2.7. Effect of Dutasteride on BPH Endpoints

The entry requirement of a PSA ≥2.5 ng/mL in REDUCE not only selected for men with an increased risk of prostate cancer, but also men at risk for BPH progression including symptoms and outcomes such as AUR and BPH-related surgery. In REDUCE, 66% of the subjects reported BPH as a current medical condition at baseline.

Dutasteride treatment showed important and clinically meaningful beneficial effects in BPH endpoints compared with placebo. These effects included:

- *Significant reduction in BPH symptoms measured by the IPSS questionnaire:* Baseline symptom scores were similar in both treatment groups, corresponding to a mild to moderate symptomatic population (8.6 in the placebo group vs. 8.7 in the dutasteride group). At each 12 month period assessed during the treatment period, the mean IPSS and mean change from baseline IPSS was higher in the placebo group than the dutasteride group, indicating a greater deterioration of prostate symptoms in the placebo group compared with the dutasteride group over the corresponding period of time (8.9 to 10.0 in the placebo group vs. 8.1 to 8.3 in the dutasteride group). The IPSS change from baseline was statistically significant at all scheduled time points from Month 6 through Month 48.
- *Reduced need for alpha blockers to treat BPH symptoms:* During the study, 18.9% of subjects in the placebo group vs. 12.7% of subjects in the dutasteride group initiated alpha blocker use, p<0.0001.
- *Improvement in urinary flow*: Baseline peak urinary flow values were similar in both treatment groups and corresponded to normal Qmax values (15.3 mL/sec in the placebo group vs. 15.2 mL/sec in the dutasteride group). Adjusted mean change from baseline in the placebo group indicated increasing deterioration in peak urinary flow during the study (-0.55 to -0.9 mL/sec). However, for the dutasteride group improvements in peak urinary flow were observed (0.27 to 0.60 mL/sec) and statistically significant differences between treatments were observed at Month 48 (-0.9 mL/sec in the placebo group vs. 0.41 mL/sec in the dutasteride group, p=0.0024).
- *Relative risk reduction in urinary tract infections:* Dutasteride treatment significantly reduced the risk of UTIs by 41% compared with placebo treatment. Overall, the incidence of UTIs was lower in the dutasteride group than the placebo group (8.8% in the placebo group vs 5.3% in the dutasteride group) (Table 33).

Table 33 First Urinary Tract Infection Event Overall (Efficacy Population)

UTI	Placebo N=4073	Dutasteride N=4049
UTI Incidence, n (%)	360 (8.8)	214 (5.3)
p-value[a]	<0.0001	
Relative Risk Estimate (95% CI)	0.59 (0.50, 0.70)	
Relative Risk Reduction % (95% CI)	40.7 (29.8, 50.0)	

a. P-value vs placebo based on log-rank test, stratified by cluster.

- *Relative risk reduction of acute urinary retention:* Dutasteride treatment significantly reduced the risk of an AUR event occurring compared with placebo treatment (6.7% placebo vs. 1.6% dutasteride). The relative risk reduction for AUR events was 77.3% for the dutasteride group compared with the placebo group (Table 34).

Table 34 AUR Events (Efficacy Population)

Time to First AUR Event	Time Period	Placebo N=4073	Dutasteride N=4049
Event (%)	Years 1-2	150 (3.7)	39 (1.0)
	Overall	272 (6.7)	63 (1.6)
Log-Rank p-value	Years 1-2	<0.0001	
	Overall	<0.0001	
Relative Risk Estimate (95% CI)	Years 1-2	0.26 (0.18, 0.37)	
	Overall	0.23 (0.17, 0.30)	
Relative Risk Reduction % (95% CI)	Years 1-2	73.9 (62.9, 81.6)	
	Overall	77.3 (70.1, 82.7)	

Relative risk reduction in BPH-related surgery: Dutasteride treatment reduced the risk of BPH-related surgery compared with placebo treatment (p<0.0001). Overall, there was a higher incidence of BPH-related surgery in the placebo group compared with the dutasteride group (5.1% placebo vs. 1.4% dutasteride). The relative risk reduction for BPH-related surgery was 73.0% for the dutasteride group compared with the placebo group (Table 35).

Table 35 BPH-Related Surgery (Efficacy Population)

Time to First BPH-related Surgery	Time Period	Placebo N=4073	Dutasteride N=4049
Surgeries, n (%)	Years 1-2	92 (2.3)	30 (0.7)
	Overall	209 (5.1)	57 (1.4)
Log-Rank p-value	Years 1-2	<0.0001	
	Overall	<0.0001	
Relative Risk Estimate (95% CI)	Years 1-2	0.33 (0.22, 0.50)	
	Overall	0.27 (0.20, 0.36)	
Relative Risk Reduction % (95% CI)	Years 1-2	66.9 (50.1, 78.1)	
	Overall	73.0 (63.8, 79.9)	

3.2.8. Health Outcomes

Most questionnaires to assess the impact of prostate cancer on subject quality of life were not developed or validated to assess the impact of Prostate cancer risk reduction on subject quality of life. Further, Prostate cancer-specific QOL was only likely to change as a result of prostate cancer diagnosis and treatment and the use of dutasteride in this trial was unlikely to impact QOL related to these events as dutasteride treatment was to be stopped at a diagnosis of Prostate cancer. Since Prostate cancer and BPH often coexist, questionnaires for subjects with BPH and/or prostatitis were used in the study.

These questionnaires include those that evaluated the impact of BPH on quality of life (IPSS QOL Q8 and BII), impact of prostatitis symptoms such as urinary symptoms and pain on quality of life (NIH CPSI), assessment of sexual function (PAS SFI), and evaluation of sleep and its quality (MOS Sleep-6S). Baseline and overall change from baseline health-related quality of life scores (HRQOL) are presented in Table 36. At

baseline, the dutasteride and placebo groups had comparable scores on all the health outcomes questionnaires.

The study demonstrated positive effects of dutasteride on subject-reported health outcomes related to the impact of BPH and prostatitis symptoms on quality of life (Table 36). There were no significant differences between dutasteride and placebo on subject-reported sleep quality. Mean decreases from baseline in scores on the PAS-SFI were higher in the dutasteride group indicating that these subjects reporting more problems with sexual function compared with placebo subjects.

Table 36 Health-Related Quality of Life scores (Efficacy Population, LOCF)

HRQOL score Change from baseline to Month 48		Placebo N= 4073	Dutasteride N= 4049
Baseline BII	Mean (SD)	2.2 (2.43)	2.2 (2.44)
BII Change from Baseline to Month 48	Mean (SD)	0.4 (2.54)	-0.2 (2.39)
	Adjusted Mean (SE)	0.44 (0.037)	-0.21 (0.037)
	p-value	<0.0001	
Baseline MOS Sleep-6S	Mean (SD)	19.0 (14.87)	18.8 (14.74)
MOS Sleep -6S Change from Baseline to Month 48	Mean (SD)	-0.2 (14.48)	-0.1 (14.79)
	Adjusted Mean (SE)	-0.03 (0.211)	0.02 (0.212)
	p-value	0.87	
Baseline NIH CPSI score	Mean (SD)	6.5 (5.27)	6.4 (5.22)
NIH CPSI Change from Baseline to Month 48	Mean (SD)	0.9 (5.48)	-0.4 (4.99)
	Adjusted Mean (SE)	0.94 (0.123)	-0.37 (0.123)
	p-value	<0.0001	
Baseline QOL Q8 score	Mean (SD)	2.1 (1.38)	2.1 (1.34)
QOL Q8 Change from Baseline to Month 48	Mean (SD)	-0.1 (1.31)	-0.3 (1.28)
	Adjusted Mean (SE)	-0.06 (0.018)	-0.33 (0.018)
	p-value	<0.0001	
Baseline PAS SFI score	Mean (SD)	8.6 (3.79)	8.6 (3.75)
PAS SFI Change from Baseline to Month 48	Mean (SD)	-0.8 (4.03)	-1.5 (4.32)
	Adjusted Mean (SE)	-0.82 (0.064)	-1.5 (0.065)
	p-value	<0.0001	

LOCF=last observation carried forward
T-tests from general linear models.

- BII=BPH Impact Index. Rates the level of BPH-associated physical discomfort, worry and interference with normal activities. Total Score range: 0-13, higher score =worse BPH related health status.
- MOS Sleep – S6=Medical Outcomes Study Sleep-6 Sleep Scale. Measures 5 aspects of sleep quality. Range 0-100, higher score = greater negative impact.
- NIH-CPSI= National Institute of Health Chronic Prostatitis Symptom Index. Measures 3 areas of prostatitis: pain, urinary symptoms and QOL impact. Range 0-43, higher sore=greater negative impact of prostatis.
- QOL Q8=Last item of the IPSS assesses QOL. Range 0-6, higher score=worse BPH-related QOL.
- PAS SFI=Problem Assessment Scale of the Sexual Function Index. Total score range 0-12, higher score=fewer problems:

3.3. Prostate Cancer in CombAT, REDEEM and other studies

A more complete description of the CombAT trial of dutasteride treatment in subjects with moderate to severe BPH is found in Section 6. Additional details about the

REDEEM trial of dutasteride treatment in subjects with low risk localized prostate cancer are found in Section 5.

CombAT: Prostate cancer AEs and biopsy data were predefined analyses in CombAT. The incidence of prostate cancer, reported as an AE, was lower in the dutasteride monotherapy (2.6%) and the combination (dutasteride/tamsulosin) therapy groups (2.3%) compared with the tamsulosin monotherapy group (3.9%; Table 37). This corresponds to a 34% and a 41% reduction of prostate cancer AEs in the dutasteride monotherapy and combination therapy groups compared with the tamsulosin monotherapy group, respectively. This was due largely to a reduction in the biopsy rate in the dutasteride monotherapy group (8.8%) and the combination therapy group (7.1%) compared with the tamsulosin monotherapy group (13.3%). PSA was the most common reason for biopsy in all groups. Among subjects undergoing a for-cause biopsy, the chances of finding a positive cancer were increased in the groups treated with dutasteride compared with the tamsulosin group Table 37.

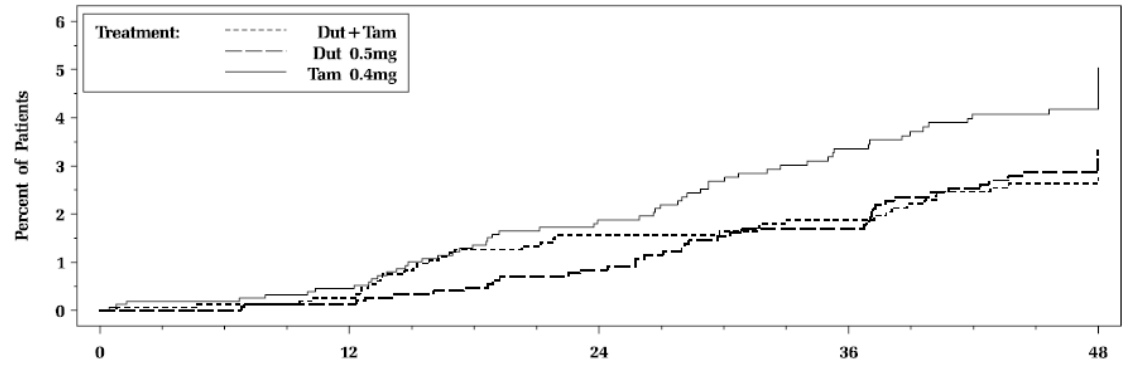
Table 37 Overview of Prostate Biopsies and Gleason Scores in CombAT (ITT Population)

	Combination N=1610	Dutasteride N=1623	Tamsulosin N=1611
Subjects biopsied, n/N (%)	115 / 1610 (7.1)	143 / 1623 (8.8)	214 / 1611 (13.3)
Subjects with prostate cancer, n (%)	37 (2.3)	42 (2.6)	63 (3.9)
Cancer-positive prostate biopsy, n/N (%)	33 / 115 (29)	40 / 143 (28)	51 / 214 (24)
Reasons for cancer-positive biopsies, n (%)	n=32	n=40	n=50
PSA	22 (69)	22 (55)	41 (82)
TRUS	5 (16)	5 (13)	3 (6)
DRE	5 (16)	11 (28)	5 (10)
Other	0	2 (5)	1 (2)
Number of cores obtained for positive biopsies, n	32	39	50
Mean (SD) [median]	10.4 (3.95) [11.0]	11.3 (6.20) [12.0]	11.0 (5.82) [10.0]
Number of cores positive for cancer, n	32	38	48
Mean (SD) [median]	3.2 (3.09) [2.0]	3.2 (2.67) [2.0]	3.1 (2.27) [2.0]
Gleason score, n (%)[a]	32	37	49
3	1 (3)	0	0
4	1 (3)	1 (3)	0
5	1 (3)	0	3 (6)
6	17 (53)	16 (43)	22 (45)
7	7 (22)	13 (35)	15 (31)
8	5 (16)	3 (8)	5 (10)
9	0	3 (8)	3 (6)
10	0	1 (3)	1 (2)
3 – 6	20 / 32 (63)	17 / 37 (46)	25 / 49 (51)
7 – 10	12 / 32 (38)	20 / 37 (54)	24 / 49 (49)
8 – 10	5 / 32 (16)	7 / 37 (19)	9 / 49 (18)

a. Gleason scores shown are for positive biopsies only.

The 4 years of treatment with dutasteride monotherapy or the combination of dutasteride and tamsulosin resulted in a significant reduction in the relative risk of Prostate cancer compared with tamsulosin monotherapy (dutasteride monotherapy: 37%, $p = 0.021$; combination therapy: 43%, $p = 0.006$; Figure 5).

Figure 5 Kaplan-Meier Estimates of the Percentage of Subjects Experiencing First Prostate Cancer AEs (CombAT ITT Population)



Dut. + Tam.				
No. of events (cumulative)	4	22	26	37
No. at risk	1610	1426	1281	1198
Dut. 0.5mg				
No. of events (cumulative)	2	12	23	42
No. at risk	1623	1462	1321	1196
Tam. 0.4mg				
No. of events (cumulative)	7	27	45	63
No. at risk	1611	1466	1275	1104

Over the 4 years of the study there were numerically fewer Gleason score 7 and Gleason score 8-10 cancers in the dutasteride groups (combination therapy and dutasteride monotherapy) compared with the tamsulosin group (Table 37). There was no evidence of an increase in Gleason score 8-10 cancers overall or during Years 3-4 in the dutasteride groups compared with tamsulosin. In Years 3-4 there were, 10 and 9 cases of Gleason score 7 cancers in the dutasteride monotherapy and tamsulosin monotherapy groups, respectively, and 7 and 6 cases of Gleason score 8-10 cancers, respectively. These results from CombAT may allow an understanding of the applicability of the REDUCE efficacy data to a broader population of men who were screened annually for prostate cancer in a way similar to screening for most men of advancing age (PSA and digital rectal examination), and in whom biopsies were performed only for clinical cause.

Other BPH Studies: In a pooled analysis of dutasteride Phase III BPH studies (N=4325 subjects), the cumulative incidence of prostate cancer, reported as an adverse event, was 51% lower over 27 months with dutasteride compared with placebo (27 subjects or 1.2% dutasteride versus 55 subjects or 2.5% placebo, p=0.002) with dutasteride as compared with placebo [Andriole, 2004].

REDEEM: The REDEEM study demonstrated that dutasteride delayed the time to progression of prostate cancer in men diagnosed with low-risk, localized disease who would otherwise receive no active therapy over 3 years (Section 5). Protocol mandated biopsies were performed at 18 months and 3 years of treatment. Similar numbers of placebo and dutasteride subjects had high-grade Gleason score 7 or 8 cancers at final biopsy. No subjects had progression to a Gleason score 9 or 10 cancer (Table 42). At the 18 month biopsy, there were 2 Gleason score 8 cancers in the placebo group and none in the dutasteride group. At the 3 year biopsy there were 3 Gleason score 8 cancers in the placebo group and 2 such cancers in the dutasteride group. REDEEM data is relevant to

the discussion around dutasteride and high grade cancers and provides additional insights into dutasteride mechanism of action and its potential impact on the rates of tumor progression and upgrading over 3 years compared to placebo in a population with low risk Prostate cancer that shared similar characteristics to those diagnosed of Prostate Cancer in REDUCE. There was no suggestion in this trial that dutasteride treatment may promote high grade cancer over a 3 yrs period.

3.4. ISUP 2005 Modified Gleason Scores

To evaluate any potential underestimation of the number of Gleason 7-10 cancers in REDUCE by use of the classic Gleason scoring methodology in the original analysis, the FDA requested an independent blinded reassessment of Gleason scoring according to the 2005 International Society of Urological Pathology (ISUP) modified Gleason scoring (modified Gleason scoring) methodology. This was performed for all available needle biopsies for first-time positive prostate cancers. See Section 2.1.3.1 and Appendix C Section 12.3 for a description of the two methods.

The reassessment of REDUCE prostate cancer needle biopsy samples by the modified Gleason scoring criteria was consistent with the classic Gleason scores in the original study report, with an overall relative risk reduction of 20.4% for dutasteride compared with placebo.

Overall, 1472 subjects out of the 1517 total number of subjects included in the REDUCE Prostate Cancer Population (97%) had first time positive biopsy samples available for review and evaluation by the independent pathologist applying the modified Gleason scoring criteria. These subjects are defined as the Reassessment Population.

Dutasteride significantly reduced the incidence of low grade cancers (modified Gleason score 2-6) compared with placebo (17.8% placebo vs. 13.2% dutasteride, $p<0.0001$, Fisher's exact test). There was no significant difference in the incidence of modified Gleason score 7-10 prostate cancers between treatment groups (6.7% placebo vs. 6.3% dutasteride).

With both scoring methods, the overall numbers of Gleason score 8-10 cancers were low (classic Gleason score: placebo: 19 subjects, dutasteride: 29 subjects; modified Gleason score: placebo: 16 subjects, dutasteride: 32 subjects). Using the classic Gleason score, the observed difference between dutasteride and placebo in the incidence of Gleason score 8-10 cancers did not reach statistical significance ($p=0.15$). Due to a net increase of 3 dutasteride subjects and a net decrease of 3 placebo subjects, using the modified Gleason score, the difference in incidence between the two treatment groups became statistically significant (0.5% placebo vs. 1.0% dutasteride, $p=0.0196$).

During Years 1-2, the incidences of Gleason score 8-10 cancers were low and similar between placebo and dutasteride with both scoring methods (classic Gleason score: placebo: 0.5%, dutasteride 0.5%; modified Gleason score: placebo: 0.5%, dutasteride 0.6%). During Years 3-4 while the incidence of these cancers was unchanged in the dutasteride group (0.6%), there was a decrease in incidence in the placebo group (0%).

Whether using the original classic Gleason score, or applying the modified Gleason score, the relative risk for detection of prostate cancer for dutasteride compared with placebo increased as the Gleason score increased (Table 20 and Table 38). The relative risk for Gleason score 6-10 cancer was 0.8 using either the classic or modified score. The relative risk of Gleason 7-10 cancers was 0.98 using the classic Gleason score and 0.94 using the modified Gleason score. For Gleason score 8-10 cancers, the relative risk was 1.58 using the classic Gleason score and 2.06 using the modified Gleason score.

Table 38 Summary of Relative Risk of Overall ISUP 2005 Modified Gleason Score (Reassessment Population)

	Modified Gleason Score[a]	Placebo N=3424 N[b]/N (%)	Dutasteride 0.5mg N=3305 N[b]/N (%)	Relative Risk[c]	Relative Risk Reduction[d] (95% CI)[e]
Overall	5 - 10	831/3388 (24.5)	641/3284 (19.5)	0.80	20.4%(12.8%, 27.4)
	6 - 10	827/3388 (24.4)	639/3284 (19.5)	0.80	20.3%(12.7%, 27.2)
	7 - 10	227/3388 (6.7)	207/3284 (6.3)	0.94	5.9%(-12.9%, 21.6)
	8 - 10	16/3388 (0.5)	32/3284 (1.0)	2.06	-106%(-275%, -13)

a. Values assessed at cancer diagnosis.
b. n= number of subjects in each treatment group.
c. Estimate is ratio of incidence values (non-stratified)
d. Estimates computed as 100 (1-Relative Risk).
e. Confidence interval based on that for the relative risk using the Wald method for the log of the incidence ratio.

There was a high level of concordance, 83%, between the original assessments done using the classic Gleason score and the reassessments using the modified Gleason score (Table 39). There were similar, but low numbers of subjects having upgraded and downgraded scores.

Table 39 Summary of Differences and Agreement between Classic and ISUP 2005 Modified Gleason Scores (Reassessment Population)

Difference: Modified Gleason Score – Classic Gleason Score	Placebo n=858	Dutasteride 0.5mg n=659	Total n=1517
N	831	641	1472
Mean	-0.0	-0.0	-0.0
SD	0.43	0.44	0.44
Median	0.0	0.0	0.0
Min.	-2	-2	-2
Max.	2	2	2
-2	1 (<1)	1 (<1)	2 (<1)
-1	73 (9)	55 (9)	128 (9)
0	690 (83)	533 (83)	1223 (83)
1	63 (8)	48 (7)	111 (8)
2	4 (<1)	4 (<1)	8 (<1)
Missing[a]	19	16	35
Scores agree, n/n (%)	690/ 831 (83)	533/ 641 (83)	1223/1472 (83)
Simple kappa Estimate	0.59	0.64	0.62
Asymptotic standard error	0.03	0.03	0.02
95% confidence interval	0.53, 0.65	0.58, 0.70	0.57, 0.66
Weighted kappa Estimate[b]	0.62	0.70	0.66
Asymptotic standard error	0.03	0.03	0.02
95% confidence interval	0.57, 0.68	0.65, 0.75	0.62, 0.70

a. No modified Gleason score provided by independent reviewer
b. Using Cicchetti-Allison Kappa coefficient weights.

Overall, concordance between classic Gleason scores and modified Gleason scores was highest in the low grade (2-6) prostate cancers. Subjects in the placebo group with classic Gleason scores of 8-10 had more downgraded modified Gleason scores than the dutasteride group (Table 40). There were few upgraded scores in either the placebo group or dutasteride group to modified Gleason score 8-10.

Table 40 Summary of Overall Gleason 2-6, 7 and 8-10 Concordance (Reassessment Population)

Treatment	Classic Gleason		ISUP 2005 Modified Gleason Score, n (%)			
	Score	N	2-6	7	8-10	Missing
Placebo	2-6[a]	617	546 (88)	57 (9)	0	14 (2)
	7	214	58 (27)	145 (68)	7 (3)	4 (2)
	8-10	19	0	9 (47)	9 (47)	1 (5)
Dutasteride. 0.5mg	2-6[a]	437	387 (89)	39 (9)	1 (<1)	10 (2)
	7	191	47 (25)	131 (69)	8 (4)	5 (3)
	8-10	29	0	5 (17)	23 (79)	1 (3)
Any treatment	2-6[a]	1054	933 (89)	96 (9)	1 (<1)	24 (2)
	7	405	105 (26)	276 (68)	15 (4)	9 (2)
	8-10	48	0	14 (29)	32 (67)	2 (4)

Note: Bolded numbers represent concordance of Classic Gleason and Modified Gleason scores
a. Almost all Gleason scores in this category were 6.

Some published literature has reported up to a 50% increase in the incidence of Gleason 7-10 cancers with the modified Gleason scoring system compared to the classic Gleason system [Helpap, 2006]. The observed high concordance between both Gleason scoring systems applied in REDUCE could be a reflection of the nature of the cancers diagnosed from a previously negative biopsy population and/or a limited presence of tertiary patterns and cribiform glands in the biopsy samples evaluated, and/or optimal alignment in pathological evaluation due to the known expertise of the pathologists performing the assessments. It was observed that there was a lesser degree of concordance with higher Gleason scores which appeared to reflect differences in interpretation of small amounts of cancer between the two pathologists, rather than inherent differences in the scoring system used. However irrespective of the possible explanations for the high level of concordance observed the outcomes support the robustness of the REDUCE study results irrespective of the method of Gleason scoring applied.

3.5. Efficacy Conclusions

Dutasteride 0.5 mg once daily for 4 years significantly reduced the risk of biopsy-detectable prostate cancer by 23% versus placebo in men at increased risk of the disease ($p<0.0001$).

- This reduction was consistent between the first two and last two years of treatment, attesting to the continued efficacy of dutasteride over time.
- The effectiveness of dutasteride in reducing the risk of prostate cancer was consistent irrespective of known risk factors (age, family history of prostate cancer, baseline PSA level), time period, and evaluation method (crude rate, modified crude rate, restricted crude rate).
- There was a highly significant reduction in low grade cancers (Gleason score ≤6) in dutasteride versus placebo treated subjects in REDUCE. Most of the prostate cancers diagnosed were low grade cancers.
- In REDUCE, dutasteride did not reduce the risk of prostate cancers with high Gleason score (Gleason 7-10) especially in those with Gleason score 7 (4+3), 8, 9 and 10.
- Overall, in REDUCE, there was a non significant increase in Gleason score 8-10 cancers in the dutasteride group compared to placebo. In Years 1 to 2 there were 18 (0.5%) and 17 (0.5%) Gleason score 8-10 cancers in the placebo group and the dutasteride group, respectively. However, in Years 3 to 4 there were fewer Gleason score 8-10 tumors in the placebo group (1, <0.1%) compared with the dutasteride group (12, 0.5%).
- Dutasteride did not interfere with the value of PSA and PSA changes to identify prostate cancer and high grade tumors. Following current dutasteride label guidance for PSA monitoring and following standard of care for placebo would identify a similar number of cancers and high grade tumors in both groups.
- Dutasteride treatment reduced the incidence of biopsy detectable prostate cancer precursor and associated lesions (HGPIN and/or Prostate cancer predictor lesions: ASAP) compared to placebo treated subjects (17% vs. 10%, respectively)

- The clinical benefits of dutasteride in men at increased risk of developing prostate cancer extended beyond prostate cancer risk reduction:
    - This risk reduction translated into fewer interventions (both surgical and non-surgical) and consequently a reduced associated burden for patients and physicians. It was related to lower total cumulative days of hospitalization.
    - Dutasteride treatment had a significant beneficial effect on BPH symptoms and related outcomes, including a reduced need for alpha blockers to treat BPH symptoms, a 77% reduction of acute urinary retention and a 73% reduction in BPH-related surgery.
    - Dutasteride treatment also reduced the incidence of UTIs by 41% compared with the placebo group and biopsy complications (4.4% dutasteride vs. 7.3% placebo) which can be frequent events in patients expected to be closely monitored.
    - QOL measures of BPH were positively affected in the dutasteride group compared with the placebo group.

4. PHARMACODYNAMIC RESULTS

4.1. Serum DHT

Mean (±SD) serum DHT at baseline was 1.4±0.99 nmol/L for the placebo group and 1.4±1.08 nmol/L for the dutasteride group within the lab normal range of 0.86-2.58 nmol/L. Mean values for serum DHT at each post-baseline visit were within the normal range for the placebo group (1.2 -1.3 nmol/L) and consistently lower in the dutasteride group (0.2-0.3 nmol/L), as expected based on dutasteride's mechanism of action. DHT values for the majority of subjects in the dutasteride group were below the quantification limit at all post-baseline assessments.

4.2. Testosterone

Mean (±SD) testosterone at baseline was comparable between the treatment groups (placebo: 15.8±6.41 nmol/L, dutasteride: 15.7±6.17 nmol/L). Mean and median testosterone values were consistently higher in the dutasteride group than in the placebo group at each post-baseline visit using the last observation carried forward (LOCF) approach, although all mean and median values were within the lab normal range of 9.02-34.7 nmol/L. Results were similar using the observed cases (OC) approach. These changes in serum testosterone concentrations are the expected result of 5α-reductase inhibition, which blocks testosterone conversion to DHT.

Adjusted mean percentage change from baseline testosterone values were significantly larger ($p<0.0001$) in the dutasteride group compared with the corresponding placebo mean values at each visit. Results were similar for the LOCF and OC approaches.

The laboratory threshold for clinical significance level for testosterone was >34.7nmol/L. Twenty-seven subjects (<1%) in the placebo group and 86 subjects (2%) in the dutasteride group had a post-baseline value above the threshold. Of those subjects with subsequent values, 100% of placebo-treated, and 86% of dutasteride-treated subjects had a subsequent value ≤34.7 nmol/L.

5. AVO105948 (REDEEM)

Note to Reader: The final study report and data for AVO105948 were submitted to the FDA on October 22, 2010 and have not been reviewed by the FDA

Data from REDEEM are briefly presented below as it is relevant to the discussion around dutasteride and high grade cancers observed in the REDUCE trial (see also Section 3.3). REDEEM provides additional insights into dutasteride mechanism of action and its potential impact on the rates of tumor progression and upgrading over 3 years compared to placebo in a population that shared similar characteristics to those diagnosed with prostate cancer in REDUCE.

5.1. Study Design

REDEEM was a 3-year, multicenter, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of dutasteride in extending the time to progression of prostate cancer. Men diagnosed with low-risk, localized disease that were candidates for or undergoing expectant management, were enrolled. Eligible subjects were randomized (1:1) to receive dutasteride 0.5mg or placebo once daily for 3 years. Transrectal ultrasound (TRUS) guided 12-core prostate biopsy was performed at 1.5 and 3 years or at the time of withdrawal if a subject discontinued early. For-cause biopsies (outside of protocol mandated biopsies) were conducted if in the judgment of the investigator, there was a clinically significant medical trigger such as rising PSA or abnormal DRE.

5.2. Study Population

5.2.1. Disposition

A total of 302 subjects were randomized. The ITT population consisted of 155 and 147 randomized subjects for the placebo and dutasteride arms of the study, respectively. The number of subjects who completed the study, including 36 months of treatment and 4 months follow-up, were 79 subjects (51%) and 102 subjects (69%) in the placebo and dutasteride groups, respectively. There were 76 placebo subjects (49%) and 45 dutasteride subjects (31%) who withdrew from the study prematurely.

5.2.2. Demography and Baseline Characteristics

Overall the study population in REDEEM represented a patient population with low-risk prostate cancer. The placebo and dutasteride treatment groups were balanced with regards to demographic characteristics. The mean subject age was 65 years, and the

proportions above and below 65 were similar in the treatment groups. Ninety percent of subjects were White. Subjects were from Canada (56%) and the United States (44%), with similar proportions in each treatment group.

5.3. Primary Endpoint

The primary endpoint of the study was time to progression of prostate cancer.

Prostate biopsy methodology

- Confirmatory review by Central Pathology was required for all entry biopsies
- Primary review by Central Pathology was required for all on-study biopsies, which included the scheduled 1.5-year and 3-year biopsies, the for-cause biopsies, and the Early End of Study biopsies. A standard of 12 cores was required for all study-mandated biopsies, including those for-cause biopsies occurring within the 6 months preceding the 1.5- and 3-year study-mandated biopsies. The modified Gleason scoring system (ISUP 2005) was used to review all study biopsies.

5.4. Efficacy Results

5.4.1. Primary Endpoint – Time to Prostate Cancer Progression

The primary endpoint of the study was the time to prostate cancer progression over a three-year study period. When a subject did not have a post-baseline biopsy nor had a therapeutic progression, the status of his prostate cancer progression was unknown. For 10 subjects in the placebo and 3 subjects in the dutasteride groups, the prostate cancer progression status was unknown for the study.

The study met its primary endpoint (log-rank p=0.007, stratified by country). Among subjects who had at least one post-baseline biopsy or had a progression (restricted crude rate approach), overall incidence of prostate cancer progression was 49% in placebo subjects and 38% in dutasteride subjects. Relative risk reduction (39%) was in favor of dutasteride over placebo using a Cox proportional hazards model stratified by country in the 3-year study period (Table 41).

In the first 1.5 years, progression occurred in 35% of placebo subjects and in 23% of dutasteride subjects (log-rank p=0.009, stratified by country). Relative risk reduction (44%) was in favor of dutasteride over placebo using a Cox proportional hazards model stratified by country. Beyond 1.5 years the incidence of progression was 24% of placebo subjects and 21% of dutasteride subjects (Table 41).

Table 41 Time to Prostate Cancer Progression in REDEEM (Restricted Crude Rate)

Parameter	Time Period	Treatment Group	
		Placebo N=155	Dutasteride N=147
Incidence of Progression, n/N (%)	First 1.5 years Beyond 1.5 years Overall	50/144 (35) 21/86 (24) 71/145 (49)	32/142 (23) 22/106 (21) 54/144 (38)
Log-rank p-value	First 1.5 years Overall		0.009 0.007
Relative risk estimate (95%CI)	First 1.5 years Overall		0.56 (0.36, 0.87) 0.61 (0.43, 0.88)
Risk reduction estimate % (95%CI)	First 1.5 years Overall		44.3 (13.1, 64.3) 38.9 (12.4, 57.4)

5.4.2. Change in Gleason Score from Baseline

5.4.2.1. Results based on final biopsy

Analysis of the change from baseline in Gleason score based on final biopsy results showed that the percentage of subjects having a higher Gleason score in the final biopsy was similar between the two treatment groups (Table 42). There were more placebo subjects than dutasteride subjects who had a Gleason score 7 at final biopsy (placebo: 19 subjects, 14%; dutasteride: 17 subjects, 12%). For cancers of Gleason score 7, both treatment groups had the same number of the more aggressive 4+3 tumors. There were 3 subjects in the placebo and 2 subjects in the dutasteride group with a Gleason score 8 in final biopsy; there were no subjects in either treatment group reporting a Gleason score 9 or 10 during the study. Table 42 provides a summary of observed Gleason scores at final biopsy in the study.

Table 42 Gleason Scores at Final Biopsy in REDEEM

		Treatment Group	
		Placebo N=155 N (%)	Dutasteride N=147 N (%)
Baseline biopsy	n GS≤6	136 136 (100)	140 140 (100)
Final biopsy	Missing (No cancer) GS≤6 GS=7 3+4 4+3 GS 8	31 (23) 83 (61) 19 (14%) 15 (11) 4 (3) 3 (2)	50 (36) 71 (51) 17 (12) 13 (9) 4 (3) 2 (1)
Change from baseline	Improvement (decrease) No change Worsened (increase)	31 (23) 83 (61) 22 (16)	50 (36) 71 (51) 19 (14)

GS=Gleason score

At the 18 month biopsy, there were 2 Gleason score 8 cancers in the placebo group and none in the dutasteride group. At the 3 year biopsy there were 3 Gleason score 8 cancers in the placebo group and 2 such cancers in the dutasteride group.

5.5. Safety

The observed safety profile for dutasteride in the REDEEM study population was consistent with the established profile in other studies of dutasteride, and no new safety issues were identified. The incidence of CV AEs was similar between the treatment groups, and there were no cardiac failure events in the dutasteride group.

5.6. Conclusion

In REDEEM, a 3-year randomized study comparing dutasteride with placebo treatment of male subjects diagnosed with low-risk, localized prostate cancer (Gleason score ≤6) who were candidates for or undergoing expectant management, there were similar numbers of upgrading to Gleason 7 and 8 cancers on subsequent biopsy in the two study arms. In addition, there were no subjects with Gleason 9-10 cancers diagnosed in either treatment group on final biopsy. Similar to the REDUCE study, biopsies in REDEEM were planned, in this case, at 18 months and 3 years of treatment. Subjects were discontinued from study medication if they experienced pathological or therapeutic progression. At the 18 month biopsy, there were 2 Gleason score 8-10 cancers in the placebo group and none in the dutasteride group. At the 3 year biopsy there were 3 Gleason score 8 cancers in the placebo group and 2 cancers in the dutasteride group. The REDEEM study supports the contention that dutasteride does not stimulate the growth of high grade cancers.

6. SUPPORTIVE STUDY ARI40005: COMBAT

CombAT is being presented for insights into prostate cancer in a study in which men are biopsied only for cause (see also Section 3.3), and for additional safety data in a large group of men exposed to dutasteride.

6.1. Study Design and Methodology

CombAT was a Phase III international, multicenter, randomized, double-blind, parallel group study. It was designed to investigate the efficacy and safety of treatment with dutasteride (0.5 mg) and tamsulosin (0.4 mg), administered once daily for 4 years, alone or in combination, on improvement of symptoms and clinical outcome in males with moderate to severe symptomatic BPH. Eligible subjects completed a 4-week placebo run-in phase followed by randomization, by center, to either 0.5 mg of dutasteride, 0.4 mg of tamulosin or 0.5 mg of dutasteride plus 0.4 mg of tamsulosin in a 1:1:1 ratio for a 4-year treatment phase. Tamsulosin as study drug was the only alpha-blocker permitted during the study. After the treatment phase, subjects entered a 4-month safety follow-up phase. The total study duration for each subject was up to 53 months.

In order to maintain investigator blinding to study treatment, PSA results of subjects treated with dutasteride were adjusted by doubling the actual value by 2 from 6 months onwards. Investigators were blinded to DHT and T results of all randomized subjects.

The study included males aged ≥50 years with clinically diagnosed moderate to severe BPH (IPSS ≥12, PV ≥30cc, PSA ≥1.5 ng/mL) at increased risk of clinical progression (composite endpoint comprising symptom deterioration by ≥4 IPSS points on 2 consecutive visits, BPH-related AUR, overflow or urge incontinence, recurrent UTI or urosepsis, and BPH-related renal insufficiency).

After prescreening, screening and baseline visits, subjects visited the clinic every 3 months. BPH efficacy assessments included per visit administration of the IPSS and BPH Impact Index, Patients Perception of Study Medication questionnaires, determination of AUR, BPH-related surgery, resource utilization, urinary tract infections (UTI), first episodes of incontinence and hematuria/hematospermia, prostate volume (measured annually via TRUS) and uroflowmetry (measured biannually).

Safety evaluations included:

- adverse events (AEs), serious adverse events (SAEs), vital signs at every clinic visit, i.e. every 3 months
- digital rectal examination (DRE), gynecomastia evaluations every 6 months
- post void residual volume every 6 months
- hematology, clinical chemistry, serum total PSA every 12 months
- ECG at screening to determine eligibility
- partner pregnancies throughout
- concomitant medications were assessed at each clinic visit, i.e. every 3 months

The disease being studied or signs/symptoms associated with the disease or disorder were not considered AEs (or SAEs) unless they were more severe than expected for the subject's condition (e.g., BPH symptoms, changes in Qmax, AUR, UTI, changes in responses to questions in the IPSS and Health Related Quality of Life [HRQOL] assessments, macroscopic hematuria/hematospermia, urinary incontinence, changes in BPH-related renal insufficiency).

Randomized subjects who were permanently discontinued from study drug were withdrawn from the study and end of treatment assessments were to be conducted. A safety follow-up visit was to be conducted 4 months later. After study drug was discontinued the subjects could consent to telephone contact for collection of clinical events every 6 months until the 4-year anniversary of randomization.

Subjects were not required to have a negative biopsy at baseline nor were any biopsies scheduled during the study. TRUS-guided, for-cause biopsies could be conducted at any

time during a subject's participation in the study if, in the judgement of the investigator, there was a clinically significant medical trigger, such as an adverse change in DRE, a clinically significant increase in serum PSA and/or nodular areas detected on TRUS. Biopsies were only reviewed at local pathology laboratories with no central pathologist involved in their evaluation. In order to maintain investigator blinding to study treatment, PSA results of subjects treated with dutasteride were adjusted by doubling the actual value by 2 from 6 months onwards.

In this study, all biopsies were independent of the study. However, if a prostate biopsy was performed and prostate cancer was detected, it was recorded as an AE and the biopsy information was collected on a case report form (CRF). Alternatively, subjects could have been diagnosed with prostate cancer by a surgical procedure and a copy of the pathology report was obtained and transcribed to a CRF. Gleason grades for these data were assigned by the pathologist who analyzed the independent biopsy sample and the method of Gleason grading was unknown but could probably include both the classic or modified Gleason scoring system. Therefore, in line with the REDUCE biopsy rereads (Section 2.1.3.1), a reassessment of Gleason scoring was to be performed to determine the modified Gleason score for first-time positive cancer diagnostic biopsies by independent blinded review, and to compare the distribution of modified Gleason scores by treatment groups (Appendix C Section 12.3).

6.2. Study Population

6.2.1. Disposition

A total of 4844 subjects were randomized to dutasteride monotherapy (1623), tamsulosin monotherapy (1611) or combination therapy (1610) for up to 4 years. The majority of subjects (>60%) completed the treatment period.

6.2.2. Baseline Demographics and Other Key Baseline Characteristics

Subjects in CombAT were predominantly White with a median age of 66.0 years. Demographic characteristics were balanced in the 3 treatment groups and were typical of a population of men with moderate to severe BPH (Table 43). The men enrolled in this study were representative of a general risk for prostate cancer population who undergo annual screening and in whom biopsies are performed for-cause. Despite different objectives and eligibility criteria between this study and REDUCE, both study populations included subjects with elevated PSA values and mean ages compatible with increased prostate cancer risk.

Table 43 CombAT Demography and Baseline Characteristics (ITT Population)

Baseline Value	Combination N=1610	Dutasteride N=1623	Tamsulosin N=1611
Age (median) years	66.0	66.0	66.0
Race (%)			
White	88	88	87
Non-White	12	12	13
Total PSA (median) ng/mL	3.4	3.4	3.6
Prostate volume (median) cc	48.9	48.4	49.6
Previous Prostate Cancer Family History (%)	9	10	8
IPSS (median)	16.0	16.0	16.0
Qmax (median) mL/sec	10.6	10.3	10.3
Prior use of Alpha Blockers (%)	50	51	51
Sexually Active (%)	73	73	72
Impotence in Past 3 Months (%)	37	36	37
Lack of Libido in Past 3 Months (%)	30	27	28

The treatment groups were similar in their past and current medical conditions (Table 44).

Table 44 Summary of Past and Current Medical Conditions Relevant to BPH (ITT Population) CombAT

		Combination N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)
Any condition		n=1609	n=1623	n=1611
	Past	243 (15)	241 (15)	245 (15)
	Current[a]	948 (59)	944 (58)	962 (60)
Any CV condition		n=1609	n=1623	n=1611
Coronary artery disease	Past	86 (5)	79 (5)	89 (6)
	Current[a]	155 (10)	149 (9)	146 (9)
Stroke	Past	38 (2)	40 (2)	34 (2)
	Current[a]	3 (<1)	1 (<1)	1 (<1)
Hypertension	Past	32 (2)	30 (2)	28 (2)
	Current[a]	651 (40)	682 (42)	671 (42)
Other CV		n=1608	n=1623	n=1611
	Past	63 (4)	68 (4)	78 (5)
	Current[a]	195 (12)	221 (14)	207 (13)
Any reproductive system condition		n=1609	n=1623	n=1611
Gynaecomastia	Past	4 (<1)	5 (<1)	5 (<1)
	Current[a]	9 (<1)	9 (<1)	5 (<1)
Other reproductive	Past	21 (1)	16 (<1)	26 (2)
	Current[a]	97 (6)	103 (6)	92 (6)
Any endocrine or metabolic condition		n=1609	n=1623	n=1611
Diabetes/glucose intolerance	Past	7 (<1)	1 (<1)	5 (<1)
	Current[a]	149 (9)	164 (10)	187 (12)
Other endocrine & metabolic	Past	23 (1)	28 (2)	21 (1)
	Current[a]	215 (13)	194 (12)	203 (13)

Subjects may be counted in multiple categories.

a. Conditions present at Screening visit

7. OVERVIEW OF SAFETY

Dutasteride is approved in more than 90 countries world-wide for treatment of BPH. After more than 7 years on the market, the estimated cumulative worldwide exposure to dutasteride exceeds 5.5 million person-years of treatment. In addition, nearly 10,000 men have been exposed to dutasteride in long-term (2-4 years) clinical trials.

The known safety profile of dutasteride in men with BPH is reflected in current product labeling:

- The most common adverse reactions in clinical trials are Impotence, Decreased libido, Ejaculation disorders, and Breast disorders (enlargement and tenderness). The incidence of Cardiac failure events observed in the REDUCE and CombAT trials is included in the Adverse Reactions section of the product labeling; no causal relationship has been established between dutasteride, alone or in combination with tamsulosin, and cardiac failure.

- Adverse reactions identified during post-approval use are Hypersensitivity reactions, including rash, pruritus, urticaria, localized edema, serious skin reactions, and angioedema. Amendments to the Adverse Reactions section of the product labeling are in progress to add information on reports of breast cancer in clinical trials and in post-marketing experience.

- Dutasteride may interfere with the formation of external genitalia in the male fetus, and for this reason carries a contraindication in pregnancy and women of child-bearing potential, a warning against handling by women who are pregnant or may become pregnant, and a warning against blood donation by patients taking dutasteride until 6 months after the last dose.

Dutasteride would be expected to present a similar safety profile in men at increased risk for prostate cancer as in men with BPH because the proposed dosing regimen is the same and the patient populations are similar.

The sNDA for prostate cancer risk reduction contained an Integrated Summary of Safety (ISS) that presented data from the REDUCE and CombAT trials, both individually and pooled. Pooling of safety data was considered appropriate as the trials were similar with respect to dutasteride dose (0.5 mg once daily), duration of treatment (4 years), timing of safety assessments, and subject demographics. Subject demographics and baseline characteristics are presented in Section 2.2.2 for REDUCE and Section 6.2.2 for CombAT. The pooled dataset included safety data from 13,075 subjects receiving the following treatments:

- Dutasteride monotherapy 0.5 mg once daily: 5728 subjects (4105 from REDUCE and 1623 from CombAT)

- Dutasteride 0.5 mg plus tamsulosin 0.4 mg once daily, combination therapy: 1610 subjects (all from CombAT)

- Placebo: 4126 subjects (all from REDUCE)

- Tamsulosin monotherapy 0.4 mg once daily: 1611 (all from CombAT).

Safety cut-off dates for the ISS were 01 December 2009 for REDUCE and 21 August 2009 for CombAT. The 120-day Safety Update to the ISS contained updated SAE and post-marketing data as of 30 April 2010.

The safety profile of dutasteride monotherapy was generally consistent between REDUCE, CombAT and the pooled analysis. This briefing document is focused on safety data from REDUCE, the pivotal study supporting the prostate cancer risk reduction indication. REDUCE was conducted in the target patient population (i.e., men at increased risk of developing prostate cancer) and was placebo-controlled, therefore allowing the clearest description of dutasteride monotherapy safety data. Data from the dutasteride monotherapy group in CombAT that are not consistent with the REDUCE data are noted.

Safety data from 2775 subjects enrolled in ARI103094, an ongoing observational study of men who had participated in REDUCE, and safety data from 276 subjects enrolled in Study AVO105948 (REDEEM) are summarized in Section 8.5 and Section 5.5, respectively.

7.1. Safety Assessments

Safety assessments included treatment-emergent AEs: all AEs, deaths, drug-related AEs, serious AEs (SAEs), AEs leading to withdrawal from study, and AEs leading to premature discontinuation of study drug. A treatment-emergent AE is defined as an AE with onset date on or after the date of randomization. AEs with missing onset dates were considered treatment-emergent. A drug-related AE is defined as an event considered by the investigator to have a reasonable possibility of being related to study drug.

AEs and SAEs were solicited by the investigators at each study visit. After giving a subject an opportunity to spontaneously mention any problems, the investigator was to inquire about AEs and SAEs by asking about any medical problems since the last visit. Diseases or conditions present or detected at baseline were not recorded as AEs or SAEs unless the condition worsened during the study.

Other safety assessments were laboratory tests (including serum PSA), vital signs, digital rectal exams, gynecomastia evaluations, and outcomes for any partner pregnancies. Electrocardiograms were collected at Baseline only.

The Safety Assessment Schedules are presented in Appendix E Section 12.5.

7.1.1. Data Presentation

AE and SAE data are displayed in order of decreasing numbers of subjects in the dutasteride group. In tables that present data by MedDRA System Organ Classes (SOCs) and preferred terms (PTs), data are ordered by SOCs followed by PTs within the SOC. For subset data, within the dutasteride group, AEs and SAEs are displayed in order of decreasing numbers of subjects in the subsets of Year 1 or Months 0-6.

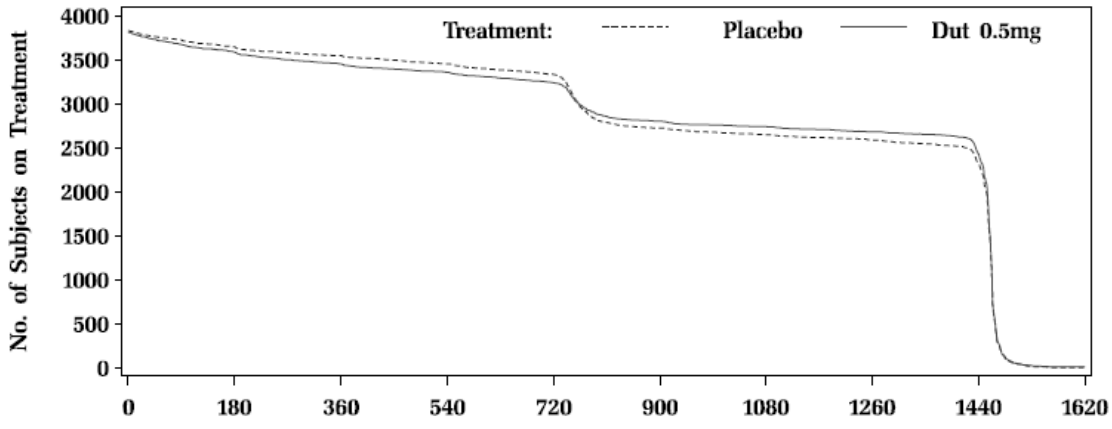
In tables with SOCs and preferred terms within SOCs, the threshold criteria for the table apply to both the SOC and the PTs. Consequently there may be SOCs in the tables that do not contain PTs. This also applies to any tables that are subsets of SOCs and PTs, e.g., AEs by time of onset.

7.2. Exposure to Study Drug and Compliance

In REDUCE, the overall median exposures to study drug were similar in the placebo and dutasteride groups (1455 and 1456 days, respectively). Most subjects (≥85%) were treated with investigational product for at least 721 days (approximately 2 years) and ≥61% were treated for greater than 1440 days (4 years). Overall compliance with taking study drug was high at ≥96% for both treatment groups. Study drug exposure over the 4 years of treatment for REDUCE is shown in Figure 6.

In CombAT, duration of exposure to study drug and compliance were similar to REDUCE.

Figure 6 Study Drug Exposure over 4 Years (REDUCE Safety Population)



Subjects on Treatment

Placebo	3827	3641	3541	3447	3329	2720	2643	2587	2324	2
Dut. 0.5mg	3811	3584	3447	3355	3235	2798	2737	2681	2424	5

7.3. AEs by Type

In REDUCE, similar percentages of subjects in the dutasteride and placebo groups reported any AEs, any SAEs, non-fatal SAEs and fatal SAEs (Table 45). The incidence

of drug-related AEs was higher in the dutasteride monotherapy group compared with the placebo group. Withdrawal rates (both AEs leading to permanent study drug discontinuation and AEs leading to withdrawal from the study) were higher for the dutasteride monotherapy group compared with placebo.

Table 45 Number (%) of Subjects with Adverse Events by Type (REDUCE Safety Population)

AE Type	Placebo N= 4126 n (%)	Dutasteride N= 4105 n (%)
Any AE	2966 (72)	3017 (73)
Any drug-related AE	604 (15)	904 (22)
Any AE leading to study drug discontinuation	244 (6)	342 (8)
Any AE leading to withdrawal from study	284 (7)	388 (9)
Any SAE	837 (20)	748 (18)
Fatal SAEs	74 (2)	70 (2)
Non-fatal SAEs	784 (19)	699 (17)
Any SAE leading to study drug discontinuation	110 (3)	115 (3)
Any SAE leading to withdrawal from study	141 (3)	141 (3)

In CombAT, percentages of subjects by type of AE for the dutasteride monotherapy group were similar to those for the dutasteride group in REDUCE with the following exception: higher percentages of subjects permanently discontinued study drug and withdrew from study due to AEs in the CombAT dutasteride monotherapy group (11% and 12%, respectively) compared with the dutasteride group of REDUCE (8% and 9%, respectively).

7.4. Common Adverse Events

The most common AEs (reported by ≥3% subjects in either group) in REDUCE were erectile dysfunction, hypertension, nasopharyngitis, back pain and influenza (Table 46). With the exception of erectile dysfunction, no clinically meaningful differences in the incidences of these common AEs were observed between the placebo and dutasteride monotherapy group.

Table 46 Number (%) of Subjects with Common AEs (>=3% in Any Group) by SOC and Preferred Term (REDUCE Safety Population)

System Organ Class Preferred term	Placebo N= 4126 n (%)	Dutasteride N= 4105 n (%)
Any AE	2966 (72)	3017 (73)
Infections and infestations	1241 (30)	1184 (29)
Nasopharyngitis	288 (7)	313 (8)
Influenza	213 (5)	204 (5)
Bronchitis	112 (3)	144 (4)
Upper respiratory tract infection	155 (4)	132 (3)
Reproductive system and breast disorders	743 (18)	948 (23)
Erectile dysfunction	363 (9)	494 (12)
Prostatitis	150 (4)	102 (2)
Gastrointestinal disorders	915 (22)	944 (23)
Diarrhoea	125 (3)	133 (3)
Inguinal hernia	114 (3)	112 (3)
Musculoskeletal and connective tissue disorders	890 (22)	898 (22)
Back pain	247 (6)	265 (6)
Arthralgia	159 (4)	176 (4)
Osteoarthritis	106 (3)	129 (3)
Pain in extremity	106 (3)	69 (2)
Nervous system disorders	530 (13)	518 (13)
Headache	127 (3)	142 (3)
Vascular disorders	469 (11)	492 (12)
Hypertension	330 (8)	355 (9)
Psychiatric disorders	386 (9)	440 (11)
Libido decreased	90 (2)	167 (4)
Metabolism and nutrition disorders	399 (10)	398 (10)
Hypercholesterolaemia	141 (3)	139 (3)
Injury, poisoning and procedural complications	461 (11)	422 (10)
Skin and subcutaneous tissue disorders	312 (8)	366 (9)
Investigations	245 (6)	316 (8)
Respiratory, thoracic and mediastinal disorders	409 (10)	343 (8)
Cough	118 (3)	87 (2)
General disorders and administration site conditions	298 (7)	312 (8)
Cardiac disorders	344 (8)	301 (7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	242 (6)	256 (6)
Renal and urinary disorders	287 (7)	247 (6)
Eye disorders	171 (4)	220 (5)
Ear and labyrinth disorders	113 (3)	110 (3)

Overall, the CombAT dutasteride monotherapy group showed similar patterns of AEs to those for the REDUCE dutasteride group. One exception was that the percentage of subjects with erectile dysfunction (12%) was slightly higher in the dutasteride group in REDUCE compared with the dutasteride monotherapy group in CombAT (9%). This finding could be explained by the differences in the populations at baseline, with the REDUCE subjects compared with the CombAT subjects being younger (median age: 63 vs. 66 years, respectively), more sexually active (81% vs. 73%, respectively), and having better sexual functioning (impotence in past 3 months: 29% vs. 36%, respectively; lack of libido in past 3 months: 22% vs. 27%, respectively).

7.4.1. Adverse Events by Intensity

Most AEs reported in REDUCE (89% in each treatment group) were mild or moderate in intensity. In each treatment group, 10% of AEs were reported as severe. Erectile dysfunction was the only AE reported as severe for 1% or more of subjects in either treatment group (placebo: 1%, dutasteride: 2%). Although infrequent overall, there were markedly fewer AEs of severe urinary retention and prostatitis in the dutasteride group than in the placebo group.

Similarly, in CombAT, most AEs (89% to 90%) reported by subjects in each treatment group were mild to moderate in intensity; severe AEs comprised 8% to 9% of all reported AEs in any treatment group.

7.4.2. Adverse Events by Time of Onset

In REDUCE the percentages of subjects reporting new onset AEs generally decreased over the 4 years of the study in both treatment groups (Appendix F Table 75). This pattern was most apparent in the 'Reproductive system and breast disorders' and 'Psychiatric disorders' SOCs and was primarily due to the lower percentages of subjects reporting erectile dysfunction and decreased libido after the first year. The percentages of subjects with AEs of erectile dysfunction and decreased libido, although low overall, were higher in the dutasteride group (6% and 3%, respectively) compared with the placebo group (3% and 1%, respectively) during the first 6 months of the study.

In CombAT, these same patterns of the highest percentages of subjects reporting sexual function AEs (erectile dysfunction and libido decreased) in Year 1 followed by declines in Year 2 were seen in the dutasteride monotherapy group. The percentage of subjects reporting erectile dysfunction in Year 1 was slightly higher in the dutasteride group of REDUCE (8%) compared with the dutasteride monotherapy group of CombAT (6%). The decline during Year 1 appeared to occur after the first 6 months of treatment in both studies (REDUCE Months 1-6 vs. Months 7-12: erectile dysfunction, 6% vs. 2% and decreased libido, 3% vs. <1%; CombAT Months 1-6 vs. Months 7-12: erectile dysfunction, 5% vs. 1% and libido decreased, 2% vs. <1%).

7.5. Drug-related Adverse Events

In REDUCE, the most common drug-related AEs in the dutasteride monotherapy group were in the 'Reproductive system and breast disorders' SOC (erectile dysfunction, gynecomastia), the 'Psychiatric disorders' SOC (libido decreased, loss of libido) and the 'Investigations' SOC (semen volume decreased). The percentages of subjects with investigator-assessed drug-related AEs of erectile dysfunction and, to a lesser extent, gynecomastia, libido decreased, loss of libido and semen volume decreased, were higher in the dutasteride monotherapy group compared with the placebo group (Table 47).

Table 47 Number (%) of Subjects with Common (>=1% in Any Group) Drug-Related AEs (REDUCE Safety Population)

System Organ Class Preferred term	Placebo N= 4126 n (%)	Dutasteride N= 4105 n (%)
Any drug-related AE	604 (15)	904 (22)
Reproductive system and breast disorders	324 (8)	548 (13)
Erectile dysfunction	237 (6)	369 (9)
Gynaecomastia	43 (1)	76 (2)
Psychiatric disorders	129 (3)	230 (6)
Libido decreased	65 (2)	137 (3)
Loss of libido	54 (1)	79 (2)
Gastrointestinal disorders	79 (2)	95 (2)
Investigations	23 (<1)	85 (2)
Semen volume decreased	9 (<1)	56 (1)
Skin and subcutaneous tissue disorders	49 (1)	62 (2)
Nervous system disorders	34 (<1)	49 (1)

The percentages of subjects reporting investigator-assessed drug-related erectile dysfunction, loss of libido and semen volume decreased were slightly higher in the dutasteride monotherapy group of REDUCE compared with the dutasteride monotherapy group of CombAT (Appendix F Table 74). This finding could be explained by the differences in the populations, with the REDUCE population being younger, more sexually active and having better sexual functioning at baseline compared to the CombAT population (Table 6 and Table 43). The percentage of subjects with drug-related libido decreased was the same for the dutasteride monotherapy groups in both studies.

7.5.1. Drug-related Adverse Events by Time of Onset

The percentage of subjects reporting initial onsets of drug-related AEs in both treatment groups in REDUCE was highest in Year 1, particularly the first 6 months, and then gradually declined throughout the remainder of the study (Table 48). Twelve percent of subjects in the dutasteride group compared with 7% of subjects in the placebo group experienced onset of a drug-related AE during the first 6 months of the study. During Month 7 through Month 12, the percentages of subjects with new onset events were 5% for the dutasteride group and 3% for the placebo group. The difference between the treatment groups during the first 6 months of the study was primarily due to increased reporting of erectile dysfunction, libido decreased and loss of libido in the dutasteride group.

Low and similar percentages of subjects in the dutasteride and placebo groups reported drug-related AEs during Years 2, 3 and 4 of the study.

These same patterns of the highest percentages of subjects in the dutasteride monotherapy groups reporting sexual function drug-related AEs (erectile dysfunction and libido decreased) in Year 1 followed by declines in Year 2 were seen in the CombAT dutasteride monotherapy group. Slightly higher percentages of subjects in the REDUCE dutasteride monotherapy group reported erectile dysfunction and libido decreased during

Year 1 compared with the CombAT dutasteride monotherapy group (erectile dysfunction: 7% vs. 5%, respectively; libido decreased: 3% vs. 2%, respectively). As in REDUCE, a decline during Year 1 appeared to occur after the first 6 months of treatment in the dutasteride monotherapy group of CombAT (erectile dysfunction: 4% vs. 1%; libido decreased: 1% vs. <1%, for Months 1-6 vs. Months 7-12, respectively).

Table 48 Subjects with Drug-Related AEs (>=1% in Any Group) by Year of Onset (REDUCE Safety Population)

System Organ Class Preferred Term	Placebo n (%)					Dutasteride n (%)				
	Month 0-6 N=4126	Month 7-12 N=3988	Year 2 N=3842	Year 3 N=3567	Year 4 N=3177	Month 0-6 N=4105	Month 7-12 N=3959	Year 2 N=3767	Year 3 N=3460	Year 4 N=3126
Any drug-related AE	269 (7)	139 (3)	148 (4)	90 (3)	50 (2)	505 (12)	211 (5)	196 (5)	101 (3)	58 (2)
Reproductive system and breast disorders	130 (3)	70 (2)	75 (2)	49 (1)	19 (<1)	277 (7)	134 (3)	103 (3)	60 (2)	29 (<1)
Erectile dysfunction	96 (2)	51 (1)	56 (1)	30 (<1)	10 (<1)	215 (5)	72 (2)	64 (2)	30 (<1)	9 (<1)
Psychiatric disorders	74 (2)	25 (<1)	24 (<1)	7 (<1)	5 (<1)	151 (4)	38 (<1)	39 (1)	9 (<1)	5 (<1)
Libido decreased	42 (1)	10 (<1)	11 (<1)	3 (<1)	1 (<1)	91 (2)	23 (<1)	21 (<1)	3 (<1)	2 (<1)
Loss of libido	29 (<1)	12 (<1)	12 (<1)	2 (<1)	2 (<1)	52 (1)	12 (<1)	15 (<1)	5 (<1)	1 (<1)
Gastrointestinal disorders	43 (1)	14 (<1)	11 (<1)	13 (<1)	6 (<1)	61 (1)	14 (<1)	14 (<1)	12 (<1)	4 (<1)

7.6. Deaths and Other Serious Adverse Events

7.6.1. Deaths

In REDUCE, 2% of subjects in each treatment group died during the study. Fatal events reported for 5 or more subjects across treatment groups are shown in Table 49, and all fatal SAEs are tabulated in Appendix F, Table 76. The most common fatal SAE was myocardial infarction/acute myocardial infarction.

Table 49 Fatal SAEs Reported for >=5 Subjects (REDUCE Safety Population)

System Organ Class Preferred Term	Placebo N=4126 n (%)	Dutasteride N=4105 n (%)
Myocardial infarction	13 (<1)	7 (<1)
Acute myocardial infarction	1 (<1)	4 (<1)
Cardiac arrest	5 (<1)	1 (<1)
Lung neoplasm malignant	5 (<1)	5 (<1)
Cerebrovascular accident	5 (<1)	3 (<1)

Seven additional deaths occurred after the AE reporting period (which ended 4 months after discontinuation of study drug) and during extended phone follow-up or in prostate cancer follow-up, which ended at the 4-year anniversary of enrollment (placebo: 5 subjects, dutasteride monotherapy: 2 subjects). Causes of death were unknown in both of the dutasteride subjects and 2 of the placebo subjects; reported causes of death in the remaining 3 placebo subjects were subdural hematoma, stroke, and cardiac problems.

In CombAT, 2% of subjects in the dutasteride monotherapy group died during the study. Myocardial infarction (MI) was also the most common fatal SAE, reported in 7 subjects in the dutasteride monotherapy group in CombAT (similar numbers were reported in the other treatment groups of CombAT). One fatal MI in the dutasteride monotherapy group was considered by the investigator as possibly related to study drug. Six additional deaths (dutasteride monotherapy: 4, combination therapy: 2) occurred after the AE reporting period of CombAT. Cause of death was not reported for these 6 cases.

7.6.2. Other Serious Adverse Events: Non-fatal Serious Adverse Events

The percentage of subjects who experienced non-fatal SAEs was similar in the dutasteride and placebo treatment group in REDUCE (Table 50). Non-fatal 'Cardiac disorder' SAEs were experienced by 4% of subjects in each group. Cardiovascular AEs are discussed in more detail in Section 7.8.2. Less than 1% of subjects in any treatment group reported individual SAEs.

A larger percentage of subjects in CombAT had non-fatal SAEs in the 'Neoplasms' SOC compared with subjects in REDUCE (4% vs. 2%, respectively), possibly due to prostate cancer only being reported as an AE/SAE if more severe than expected in REDUCE.

Table 50 Non-Fatal SAEs Reported for >=10 Subjects in Any Group (REDUCE Safety Population)

System Organ Class[a] Preferred term	Placebo N= 4126 n (%)	Dutasteride N= 4105 n (%)
Any non-fatal SAE	784 (19)	699 (17)
Cardiac disorders	176 (4)	155 (4)
Coronary artery disease	22 (<1)	35 (<1)
Myocardial infarction	30 (<1)	31 (<1)
Atrial fibrillation	21 (<1)	18 (<1)
Angina pectoris	35 (<1)	14 (<1)
Cardiac failure	3 (<1)	10 (<1)
Coronary artery stenosis	10 (<1)	8 (<1)
Arrhythmia	16 (<1)	5 (<1)
Gastrointestinal disorders	95 (2)	104 (3)
Inguinal hernia	28 (<1)	31 (<1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	103 (2)	95 (2)
Colon cancer	10 (<1)	10 (<1)
Nervous system disorders	77 (2)	87 (2)
Cerebrovascular accident	14 (<1)	19 (<1)
Transient ischaemic attack	13 (<1)	8 (<1)
Musculoskeletal and connective tissue disorders	68 (2)	82 (2)
Osteoarthritis	26 (<1)	39 (<1)
Injury, poisoning and procedural complications	83 (2)	80 (2)
Infections and infestations	137 (3)	73 (2)
Pneumonia	24 (<1)	21 (<1)
Sepsis	17 (<1)	2 (<1)
Appendicitis	12 (<1)	2 (<1)
Vascular disorders	49 (1)	47 (1)
Hypertension	10 (<1)	8 (<1)
Renal and urinary disorders	59 (1)	40 (<1)
Calculus ureteric	5 (<1)	11 (<1)
Urinary retention	17 (<1)	3 (<1)
Respiratory, thoracic and mediastinal disorders	49 (1)	27 (<1)
Pulmonary embolism	10 (<1)	5 (<1)
Hepatobiliary disorders	30 (<1)	27 (<1)
Cholelithiasis	10 (<1)	16 (<1)
General disorders and administrative site conditions	18 (<1)	19 (<1)
Blood and lymphatic system disorders	6 (<1)	18 (<1)
Reproductive system and breast disorders	37 (<1)	15 (<1)
Prostatitis	18 (<1)	1 (<1)
Benign prostatic hyperplasia	10 (<1)	5 (<1)
Metabolism and nutrition disorders	7 (<1)	13 (<1)
Eye disorders	13 (<1)	10 (<1)
Psychiatric disorders	12 (<1)	10 (<1)

Only SOCs with ≥ 10 subjects with non-fatal SAEs in either treatment group are included.

7.7. AEs Leading to Permanent Discontinuation from Study Drug and AEs Leading to Withdrawal from Study

7.7.1. AEs Leading to Permanent Discontinuation of Study Drug

7.7.1.1. Common AEs Leading to Permanent Discontinuation of Study Drug

In REDUCE, 8% of subjects in the dutasteride group and 6% of subjects in the placebo group experienced an AE that led to permanent discontinuation of study drug (Table 51). With the exception of erectile dysfunction, libido decreased, and gynecomastia, AEs leading to permanent discontinuation of study drug were reported with similar frequency in both treatment groups.

Table 51 AEs Leading to Permanent Discontinuation of Study Drug Reported by at Least 5 Subjects in Any Group (REDUCE Safety Population)

Preferred term	Placebo N=4126 n (%)	Dutasteride N=4105 n (%)
Any AE leading to permanent discontinuation of study drug	244 (6)	342 (8)
Reproductive system and breast disorders	36 (<1)	97 (2)
Erectile dysfunction	28 (<1)	66 (2)
Gynaecomastia	2 (<1)	15 (<1)
Nipple pain	1 (<1)	5 (<1)
Sexual dysfunction	0	5 (<1)
Psychiatric disorders	29 (<1)	58 (1)
Libido decreased	10 (<1)	27 (<1)
Loss of libido	11 (<1)	16 (<1)
Depression	3 (<1)	6 (<1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	52 (1)	47 (1)
Lung neoplasm malignant	10 (<1)	6 (<1)
Prostate cancer	2 (<1)	5 (<1)
Metastases to liver	5 (<1)	1 (<1)
Cardiac disorders	26 (<1)	34 (<1)
Myocardial infarction	10 (<1)	10 (<1)
Gastrointestinal disorders	22 (<1)	34 (<1)
Diarrhoea	1 (<1)	6 (<1)
Abdominal pain upper	5 (<1)	4 (<1)
Nervous system disorders	30 (<1)	32 (<1)
Headache	4 (<1)	6 (<1)
Cerebrovascular accident	4 (<1)	5 (<1)
Dizziness	6 (<1)	4 (<1)
Skin and subcutaneous tissue disorders	18 (<1)	25 (<1)
Rash	2 (<1)	9 (<1)
General disorders and administration site conditions	10 (<1)	22 (<1)
Fatigue	3 (<1)	6 (<1)
Asthenia	2 (<1)	5 (<1)
Investigations	5 (<1)	16 (<1)
Semen volume decreased	1 (<1)	8 (<1)
Vascular disorders	6 (<1)	15 (<1)
Respiratory, thoracic and mediastinal disorders	11 (<1)	12 (<1)
Dyspnoea	5 (<1)	5 (<1)
Musculoskeletal and connective tissue disorders	2 (<1)	10 (<1)

Preferred term	Placebo N=4126 n (%)	Dutasteride N=4105 n (%)
Renal and urinary disorders	16 (<1)	8 (<1)
Urinary retention	5 (<1)	0
Injury, poisoning and procedural complications	6 (<1)	6 (<1)
Blood and lymphatic system disorders	2 (<1)	6 (<1)
Infections and infestations	10 (<1)	5 (<1)
Hepatobiliary disorders	6 (<1)	5 (<1)

Only SOCs with ≥5 subjects with AEs in either group are included.

The initial onset of most AEs leading to permanent discontinuation of study drug occurred during the first year of the study, especially during the first 6 months of treatment in both treatment groups. The most common AEs leading to permanent discontinuation of study drug during the first 6 months of treatment were in the 'Reproductive system and breast disorders' and 'Psychiatric disorders ' SOCs. The largest difference between the 2 groups in AEs leading to discontinuation of study drug was reported for erectile dysfunction during the first 6 months as 1% of subjects in the dutasteride monotherapy group reported this AE compared with <1% of subjects the placebo group. All other AEs were reported by <1% of subjects in each treatment group.

In CombAT, a higher percentage of subjects in the dutasteride monotherapy group experienced AEs leading to permanent discontinuation of study drug compared with dutasteride subjects in REDUCE (11% vs. 8%, respectively). However, a higher percentage of subjects discontinued study drug due to erectile dysfunction in the dutasteride group in REDUCE (2%) than in the dutasteride monotherapy group in CombAT (<1%). In both studies, all other individual AEs leading to permanent discontinuation of study drug were reported by <1% of subjects, with the exception of prostate cancer in CombAT (2% in dutasteride monotherapy group). This difference is likely due to the requirement that prostate cancer not be considered an AE in REDUCE, unless it was more severe than expected.

Generally, the dutasteride group in REDUCE and and the dutasteride monotherapy group in CombAT were similar to one another in AEs leading to permanent discontinuation of study drug over time, with minor exceptions. In Year 1, a higher percentage of dutasteride subjects in REDUCE than dutasteride monotherapy subjects in CombAT discontinued study drug due to 'Reproductive system and breast disorders' (2% vs. <1%) with erectile dysfunction as the primary AE (1% vs. <1%) leading to discontinuation of study drug. All other AEs leading to permanent discontinuation of study drug were reported by <1% of subjects during Months 1 to 6 and Months 7 to 12 in the dutasteride group in REDUCE and the dutasteride monotherapy group in CombAT.

7.7.1.2. Drug-Related AEs Leading to Permanent Discontinuation of Study Drug

In REDUCE, the percentage of subjects permanently discontinued from study drug because of investigator-assessed drug-related AEs was low. More subjects in the dutasteride group compared with the placebo group reported drug-related AEs that led to permanent discontinuation of study drug (4% vs. 2%, respectively). All drug-related AEs leading to permanent discontinuation were reported by <1% of subjects in either

treatment group with the exception of erectile dysfunction, which was reported by 2% of subjects in the dutasteride group and <1% of subjects in the placebo group.

In CombAT, fewer subjects in the dutasteride monotherapy group were permanently discontinued from study drug due to drug-related AEs in the 'Reproductive system and breast disorders' SOC compared to the dutasteride group in REDUCE (1% vs. 2%, respectively) with erectile dysfunction as the primary drug-related AE leading to permanent discontinuation of study drug (<1% vs. 2%, respectively).

7.7.2. AEs Leading to Withdrawal from the Study

7.7.2.1. Common AEs Leading to Withdrawal from the Study

In REDUCE, overall there was little difference between the percentages of subjects who were withdrawn from the study due to AEs (placebo: 7%, dutasteride: 9%) and the percentage of subjects who were permanently discontinued from study drug due to AEs. With the exception of erectile dysfunction (placebo: <1%, dutasteride: 2%), most AEs leading to withdrawal from the study drug were reported with similar frequency (<1%) in both treatment groups.

Again, the initial onset of most AEs leading to withdrawal from the study occurred during the first year of the study, especially during the first 6 months of treatment. The largest difference between the 2 groups in AEs leading to withdrawal from the study was reported for erectile dysfunction during the first 6 months as 1% of subjects in the dutasteride monotherapy group reported this AE compared with <1% of subjects the placebo group. All other AEs were reported by <1% of subjects in each treatment group.

7.7.2.2. Drug-Related AEs Leading to Withdrawal from the Study

In REDUCE, more subjects in the dutasteride group compared with the placebo group reported drug-related AEs that led to withdrawal from the study (5% vs. 2%, respectively). All drug-related AEs leading to withdrawal were reported by <1% of subjects in either treatment group with the exception of erectile dysfunction which was reported by 2% of subjects in the dutasteride group and <1% of subjects in the placebo group.

In CombAT, there was a higher percentage of subjects in the dutasteride monotherapy group withdrawn from study due to AEs (12%) compared with the REDUCE dutasteride group (9%). However, for individual AEs, more subjects were withdrawn from the study due to erectile dysfunction for all AEs, drug-related AEs and during the first 6 months of treatment in REDUCE compared with CombAT (2% vs. <1% for both all AEs and drug-related AEs; 1% vs. <1% during first 6 months of treatment for REDUCE vs. CombAT, respectively). In both studies, the percentage of subjects withdrawn for all other AEs, with the exception of prostate cancer, was <1%. The AE of prostate cancer resulted in the withdrawal of 2% of subjects in the dutasteride monotherapy group in CombAT and <1% of subjects in the dutasteride group of REDUCE. However, prostate cancer was not reported as an AE in REDUCE unless it was more severe than expected. Subjects in

CombAT who were diagnosed with prostate cancer were withdrawn from the study, while in REDUCE they were discontinued from study drug, but could remain in the study

7.8. AEs of Special Interest

There were two general categories of AEs of special interest in REDUCE and CombAT, sexual function AEs and cardiovascular events. Sexual function AEs (i.e., altered [decreased] libido, impotence, ejaculation disorders) and breast disorders (enlargement and tenderness), are known class effects of 5ARIs. Cardiovascular events were designated and analyzed as events of special interest in response to a request from regulatory authorities, received while REDUCE and CombAT were ongoing, to include cardiovascular events in the risk management plan.

These AEs of special interest were collected in the same manner as all other AEs, but were summarized and analyzed using composite AE terms, which pool together related MedDRA preferred terms (Table 52). These composite terms were defined prospectively in the analysis plans for both studies.

Table 52 MedDRA Dictionary Coding for Adverse Events of Special Interest

Composite Term	MedDRA Preferred Term
Reproductive system and breast disorders AEs of Special Interest	
Altered (decreased) libido	Libido decreased, libido disorder, loss of libido, sexual dysfunction, male sexual dysfunction
Impotence	Erectile dysfunction, disturbance in sexual arousal, psychogenic erectile dysfunction, organic erectile dysfunction
Ejaculation disorders	Anorgasmia, retrograde ejaculation, semen volume decreased, male orgasmic disorder, orgasmic sensation decreased, orgasm abnormal, ejaculation delayed, ejaculation disorder, ejaculation failure, premature ejaculation
Breast Disorders	
Breast Enlargement	Breast hyperplasia, breast enlargement, gynecomastia, nipple disorder, breast engorgement, breast swelling
Breast Tenderness	Breast pain, breast tenderness, nipple pain, nipple swelling, breast discomfort
Prostate cancer	Prostate cancer, prostate cancer stage 0 – IV, prostate cancer recurrent
Cardiovascular AEs of Special Interest	
Acute Coronary Syndrome	Acute myocardial infarction, myocardial infarction, silent myocardial infarction, sudden cardiac death, angina unstable, cardiac arrest, cardio-respiratory arrest, cardiac death, acute coronary syndrome
Ischemic Cerebrovascular Events	Cerebrovascular accident, transient ischemic attack, cerebral infarction, cerebrovascular disorder, cerebral artery embolism, cerebral artery occlusion, cerebral artery thrombosis, ischemic stroke, cerebral circulatory failure, cerebellar infarction, thalamic infarction, reversible ischemic neurologic deficit, thrombotic stroke, embolic stroke, vertebral artery occlusion, carotid arterial embolus, carotid artery occlusion, carotid artery stenosis, carotid artery thrombosis, thrombotic cerebral infarction, brain stem infarction, embolic cerebral infarction, lacunar infarction, brain stem stroke, stroke in evolution, ischaemic cerebral infarction
Cardiac Failure	Cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left ventricular failure acute, right ventricular failure, right ventricular failure acute, ventricular failure, cardiopulmonary failure, congestive cardiomyopathy
Ischemic Coronary Artery Disorders/Atherosclerosis	Coronary artery embolism, coronary artery occlusion, coronary artery stenosis, coronary artery thrombosis, myocardial ischemia, coronary artery disease, arteriosclerosis coronary artery
Cardiac Arrhythmias	Ventricular extrasystoles, torsade de pointes, ventricular fibrillation, cardiac fibrillation, electromechanical dissociation, ventricular asystole, long QT syndrome, ventricular tachycardia, ventricular arrhythmia, ventricular flutter
Peripheral Vascular Disease	Deep vein thrombosis

7.8.1. Reproductive System and Breast Disorder Adverse Events of Special Interest and Prostate Cancer

Table 53 summarizes the incidence and relative risk of reproductive system and breast disorder AEs of special interest as composite AE terms over the four years of the REDUCE trial. A significantly greater risk was observed in the dutasteride group compared with the placebo group for composite term AEs of impotence, altered libido, ejaculation disorders and breast disorders and is consistent with data from previous studies. Although not defined as an event of special interest, there were no cases of male breast cancer in REDUCE.

Table 53 Overview of Reproductive System and Breast Disorder Special Interest AEs (REDUCE Safety Population)

Composite Term	Placebo N= 4126 n (%)	Dutasteride N= 4105 n (%)	Relative Risk Estimate[a] (95% CI) Dutasteride vs. Placebo
Impotence	364 (8.8)	495 (12.1)	1.42 (1.24, 1.62)*
Altered (decreased) libido	168 (4.1)	282 (6.9)	1.73 (1.43, 2.09)*
Breast disorders	86 (2.1)	159 (3.9)	1.89 (1.46, 2.46)*
Breast enlargement	60 (1.5)	108 (2.6)	1.84 (1.34, 2.52)*
Breast tenderness	35 (0.8)	75 (1.8)	2.19 (1.46, 3.27)*
Ejaculation disorders	47 (1.1)	144 (3.5)	3.15 (2.27, 4.38)*

*Statistically significant ($p \leq 0.0001$); p-value based on log rank test

a. Relative risk (hazard ratio) based on Cox proportional hazards model

Nearly all AEs related to sexual function and breast disorders were non-serious. There was one subject with ejaculation disorder rated as serious and one subject with breast enlargement rated as serious; both subjects were in the dutasteride group.

Most of the subjects with sexual function and breast disorder AEs had events rated mild or moderate in intensity. The proportions of subjects with severe impotence were 1.2% (49/4126) in the placebo group and 1.3% (55/4105) in the dutasteride group. For all other events, the proportions of subjects with severe events were <1% in both treatment groups.

Although withdrawal from REDUCE due to sexual function and breast disorder events was more common in the dutasteride group than the placebo group, withdrawal due to these events was infrequent, with 1.2%, 1.6%, 0.4%, and 0.5%, respectively, of dutasteride-treated subjects withdrawing from the study due to their initial event of altered (decreased) libido, impotence, ejaculation disorders, and breast disorders, compared to 0.6%, 0.7%, <0.1%, 0.1%, respectively,in the placebo group.

Most of the sexual function AEs remained unresolved, but of those that were resolved, more than half resolved on therapy (Table 54).

Table 54 Outcomes of Reproductive System and Breast Disorder Special Interest AEs (REDUCE Safety Population)

Composite AE Term		Placebo N= 4126 n (%)	Dutasteride N= 4105 n (%)
Any altered (decreased) libido event, n (%)		168 (4.1)	282 (6.9)
Outcome, n/N[a] (%)	Resolved[b]	47/164 (29)	83/278 (30)
	On therapy	36/47 (77)	42/83 (51)
	Off therapy	11/47 (23)	41/83 (49)
Any impotence event, n (%)		364 (8.8)	495 (12.1)
Outcome, n/N[a] (%)	Resolved[b]	77/352 (22)	119/487 (24)
	On therapy	60/77 (78)	80/119 (67)
	Off therapy	17/77 (22)	39/119 (33)
Any ejaculation disorder event, n (%)		47 (1.1)	144 (3.5)
Outcome, n/N[a] (%)	Resolved[b]	13/45 (29)	32/143 (22)
	On therapy	9/13 (69)	18/32 (56)
	Off therapy	4/13 (31)	14/32 (44)
Any breast disorder event, n (%)		86 (2.1)	159 (3.9)
Outcome, n/N[a] (%)	Resolved[b]	41/84 (49)	92/156 (59)
	On therapy	31/41 (76)	67/92 (73)
	Off therapy	10/41 (24)	25/92 (27)

a. n/N=number of subjects with the outcome/number of subjects with events

b. Resolved or resolved with sequelae

Note: All summaries are in terms of the initial event,

Table 55 shows the numbers and percentages of subjects in each REDUCE treatment group with drug-related (investigator assessment) sexual AEs and breast disorders. Subjects in both treatment groups reported the highest percentage of drug-related AEs of special interest during the first 6 months of the study. In the dutasteride group, the proportions of subjects with new onset of each AE decreased over years 2 to 4 of the study, with less than 1% of subjects reporting new onset of any of these AEs in Year 3 or Year 4. The types and frequencies of drug-related AEs in REDUCE are consistent with previous studies and current labeling.

Table 55 Drug-Related Reproductive System and Breast Disorder Special Interest AEs Reported for at Least 1% of Subjects and More Frequently in the Dutasteride Group than in the Placebo Group, by Time of Onset (REDUCE Safety Population)

	AE Time of Onset				
	Year 1		Year 2	Year 3	Year 4
Composite AE Term	Month 0-6	Month 7-12			
Dutasteride	N=4105	N=3959	N=3767	N=3460	N=3126
Placebo	N=4126	N=3988	N=3842	N=3567	N=3177
Impotence					
Dutasteride	216 (5.3)	72 (1.8)	64 (1.7)	30 (0.9)	9 (0.3)
Placebo	96 (2.3)	51 (1.3)	56 (1.5)	31 (0.9)	10 (0.3)
Decreased libido					
Dutasteride	153 (3.7)	39 (1.0)	37 (1.0)	10 (0.3)	4 (0.1)
Placebo	76(1.8)	23 (0.6)	26 (0.7)	6 (0.2)	3 (<0.1)
Ejaculation disorders					
Dutasteride	57 (1.4)	35 (0.9)	22 (0.6)	2 (<0.1)	4 (0.1)
Placebo	11 (0.3)	6 (0.2)	7 (0.2)	3 (<0.1)	1 (<0.1)
Breast disorders					
Dutasteride	39 (1.0)	37 (0.9)	33 (0.9)	25 (0.7)	16 (0.5)
Placebo	25 (0.6)	15 (0.4)	13 (0.3)	13 (0.4)	9 (0.3)

In CombAT, lower proportions of subjects in the dutasteride monotherapy group had sexual AEs compared to the REDUCE dutasteride group: impotence (9.1% vs. 12.1%), altered (decreased) libido (5.4% vs. 6.9%), and ejaculation disorders (2.5% vs. 3.5%). A slightly higher proportion of subjects in the CombAT dutasteride monotherapy group had breast disorders compared to the REDUCE dutasteride group (4.1% vs. 3.9%).

7.8.2. Cardiovascular Events

7.8.2.1. REDUCE

The proportions of subjects with AEs coded to the 'Cardiac disorders' SOC was similar across treatment groups: 8% in the placebo group and 7% in the dutasteride group (Table 46). In both groups, the most common AE in the 'Cardiac Disorders' SOC was angina pectoris (dutasteride 1% and placebo 2%). Serious 'Cardiac disorders' were reported for 5% subjects in the placebo group and 4% subjects in the dutasteride group.

In each treatment group, 25 subjects (<1%) experienced a fatal 'Cardiac Disorders' SAE. The most common fatal SAE was myocardial infarction (<1% in each group). All fatal SAEs are tabulated in Appendix F Table 76.

Table 56 summarizes the incidence and relative risk of cardiovascular AEs of special interest as composite AE terms over the four years of the REDUCE trial. A greater risk was observed in the dutasteride group compared with the placebo group for composite term AE of cardiac failure (dutasteride, 0.7% and placebo, 0.4%; log-rank p=0.03; Relative Risk [95% CI], 1.91 [1.04, 3.50]). The proportions of subjects with any cardiovascular event of interest and with other individual composite events of interest were similar between treatment groups.

Table 56 Number (%) of Subjects with Cardiovascular Events of Interest (REDUCE Safety Population)

Cardiovascular Event of Interest (Composite Term)	Placebo (N=4126) n (%)	Dutasteride (N=4105) n (%)	Relative Risk[a] (95% CI)
Any Cardiovascular Event of Interest	212 (5.1)	223 (5.4)	1.06 (0.88, 1.28)
Ischaemic Coronary Artery Disorders/Atherosclerosis	68 (1.6)	78 (1.9)	1.15 (0.83, 1.60)
Acute Coronary Syndrome	73 (1.8)	61 (1.5)	0.83 (0.59, 1.17)
Cardiac Failure	16 (0.4)	30 (0.7)	1.91 (1.04, 3.50)
Cardiac Arrhythmias	9 (0.2)	7 (0.2)	0.78 (0.29, 2.10)
Peripheral Vascular Disease	11 (0.3)	11 (0.3)	1.02 (0.44, 2.35)
Ischemic Cerebrovascular Events	53 (1.3)	58 (1.4)	1.11 (0.77, 1.61)

a. Relative risk (hazard ratio) based on Cox proportional hazards model

As shown in Table 52, the composite term ‘cardiac failure’ contains related, but not interchangeable, MedDRA preferred terms, some of which describe congestive heart failure; other terms are non-specific and may describe congestive heart failure or another medical condition. The difference between treatment groups for ‘cardiac failure’ is due primarily to the difference in numbers of subjects with the non-specific preferred term ‘cardiac failure’ (16 dutasteride subjects compared with 8 placebo subjects) (Table 57). Review of case narratives for events described with the non-specific term ‘cardiac failure’ showed that in both treatment groups, some events were consistent with congestive heart failure, while others were consistent with either heart failure due to underlying atrial arrhythmias or some other terminal event that lead to cardiopulmonary arrest, such as lung cancer, stroke with pneumonia, or unwitnessed deaths.

Table 57 Number (%) of Subjects with Cardiac Failure Adverse Events (REDUCE Safety Population)

Composite Term MedDRA Preferred Term	Placebo n (%) N=4126	Dutasteride n (%) N=4105
Any Cardiac Failure AE	16 (0.4)	30 (0.7)
Cardiac Failure	8 (0.2)	16 (0.4)
Cardiac failure congestive	5 (0.1)	8 (0.2)
Cardiac failure acute	1 (<0.1)	3 (<0.1)
Congestive cardiomyopathy	2 (<0.1)	1 (<0.1)
Cardiogenic shock	0	1 (<0.1)
Left ventricular failure	1 (<0.1)	0
Cardiopulmonary failure	0	1 (<0.1)

Among the 30 subjects in the dutasteride group with composite events of ‘cardiac failure, none of the events was assessed by the investigator as related to study drug. Among the 16 placebo subjects, two cardiac failure events (in the same subject) were assessed by the investigator as drug-related.

Review of subject narratives showed that all but 2 of the 30 dutasteride-treated subjects and all of the 16 placebo-treated subjects had at least one contributory concurrent medical event or past medical history (e.g., coronary artery disease, hypertension, cardiac arrhythmias) that placed them at increased risk of cardiac failure. The difference in incidence of cardiac failure was not explained by differences in demographic/baseline characteristics. As shown in Section 2.2.2, the dutasteride and placebo treatment groups were balanced with respect to age, race, and past/current medical conditions, including hypertension, coronary artery disease, other cardiovascular conditions, and diabetes. Body mass index at baseline (Table 63) and tobacco use (39%-40% former users, 15% current users) were also similar between treatment groups. Use of concomitant medications during the 4 years was similar between treatment groups, with the exception of alpha blockers, which were used by more subjects in the placebo group (34%) compared with the dutasteride group (28%). Cardiovascular medications were the most frequently used (72% of total subjects). In both treatment groups, there was frequent use of concomitant medications with potential cardiovascular effects, including effects on blood pressure and cardiac function: angiotensin-converting enzyme inhibitors (34%-36%), diuretics (21%-22%), beta blockers (21%-22%), and calcium antagonists (14%-16%).

Proportional hazards regression modeling showed that higher age, higher heart rate at baseline, other past cardiovascular conditions, any current cardiovascular condition, and any use of 4-quinolones before heart failure were significantly related to cardiac failure; however, the relative risk estimate in the presence of these significant baseline parameters remained relatively unchanged (relative risk: 1.90, 95% CI: 1.04, 3.49).

Notably, there were no differences between treatment groups in incidences of events that may trigger cardiac failure such as myocardial infarction, myocardial ischemia, atrial fibrillation, or other arrhythmias. In addition, there were no differences between treatment groups in incidences of AEs consistent with congestive heart failure (e.g., dyspnea, peripheral edema, pulmonary edema, orthopnea).

In a *post-hoc* analysis of concomitant *alpha blocker use* in REDUCE, there was a higher incidence of the composite term ‘cardiac failure’ in subjects taking dutasteride and an alpha blocker concomitantly (12/1152, 1.0%) compared with dutasteride and no alpha blocker (18/2953, 0.6%), placebo and an alpha blocker (1/1399, <0.1%), or placebo and no alpha blocker (15/2727, 0.6%). However, as alpha blocker use was not randomized in REDUCE, and this study was not a designed to detect such differences in treatment groups, the significance of this finding is unclear.

7.8.2.2. CombAT

The proportions of subjects with any cardiovascular event of interest and with individual composite events of interest were similar among the three treatment groups with the exception of the composite term “cardiac failure”(dutasteride + tamsulosin combination therapy group, 0.9%. dutasteride monotherapy group, 0.2% and tamsulosin monotherapy group 0.6%, Relative risk [95% CI] 3.57 [1.17, 10.8] for combination vs. dutasteride monotherapy and 1.36 [0.61, 3.07] for combination vs. tamsulosin monotherapy) (Table 58).

Table 58 Number (%) of Subjects with Cardiovascular Events of Interest (CombAT ITT Population)

Cardiovascular Event of Interest (Composite Term)	Dut + Tam (N=1610) n (%)	Dutasteride (N=1623) n (%)	Tamsulosin (N=1611) n (%)
Any Cardiovascular Event of Interest	96 (6.0)	95 (5.9)	92 (5.7)
Ischaemic Coronary Artery Disorders/Atherosclerosis	35 (2.2)	36 (2.2)	32 (2.0)
Acute Coronary Syndrome	30 (1.9)	32 (2.0)	28 (1.7)
Cardiac Failure	14 (0.9)	4 (0.2)	10 (0.6)
Cardiac Arrhythmias	3 (0.2)	5 (0.3)	6 (0.4)
Peripheral Vascular Disease	2 (0.1)	2 (0.1)	1 (<0.1)
Ischemic Cerebrovascular Events	24 (1.5)	28 (1.7)	24 (1.5)

Dut=dutasteride; Tam=tamsulosin

As in REDUCE, the difference among treatment groups for 'cardiac failure' is due primarily to differences in the numbers of subjects with the non-specific preferred term 'cardiac failure' (9 subjects in the combination group, 1 subject in the dutasteride monotherapy group, and 6 subjects in the tamsulosin monotherapy group) (Table 59). Review of case narratives for events described with the non-specific term 'cardiac failure' showed that in all treatment groups, some events were consistent with congestive heart failure, while others were consistent with either heart failure due to atrial arrhythmias or some other terminal event that lead to cardiopulmonary arrest, such as ruptured aortic aneurysm (thoracic), interstitial lung disease, or unwitnessed death.

Table 59 Number (%) of Subjects with Cardiac Failure Adverse Events (CombAT ITT Population)

Composite Term MedDRA Preferred Term	Dut + Tam (N=1610) n (%)	Dutasteride (N=1623) n (%)	Tamsulosin (N=1611) n (%)
Any Cardiac Failure AE	14 (0.9)	4 (0.2)	10 (0.6)
Cardiac Failure	9 (0.6)	1 (<0.1)	6 (0.4)
Cardiac failure congestive	6 (0.4)	1 (<0.1)	2 (0.1)
Left ventricular failure	0	0	2 (0.1)
Cardio-pulmonary failure	0	1 (<0.1)	0
Congestive cardiomyopathy	0	0	1 (<0.1)
Acute left ventricular failure	0	1 (<0.1)	0

Dut=dutasteride; Tam=tamsulosin

None of the events of the composite term cardiac failure in any treatment group were assessed by the investigator as related to study drug. Review of subject narratives showed that all but 1 subject (dutasteride group) with cardiac failure had at least one contributory concurrent medical event or past medical history that placed them at increased risk of cardiac failure (e.g., coronary artery disease, hypertension, cardiac arrhythmia).

As in REDUCE, the difference in incidence of cardiac failure between the combination group and the dutasteride group was not explained by differences in demographic/baseline characteristics. As shown in Section 6.2.2., the treatment groups were balanced with respect to age, race, and past current medical conditions, including cardiovascular conditions and endocrine or metabolic conditions. Tobacco use was similar across groups (35%-89%) subjects took at least one concomitant medication during the study, and usage of concomitant medications was similar across the treatment groups. In all treatment groups, there was frequent use of concomitant medications with potential effects on the cardiovascular system, including effects on blood pressure and cardiac function: angiotensin-converting enzyme inhibitors (37%), diuretics (22%), beta blockers (24%-27%), and calcium antagonists (18%-21%).

Proportional hazards regression modeling showed that past and current condition of coronary artery disease and any use of diuretics before cardiac failure were significant effects for time to first cardiac failure; however, the relative risk estimate for combination therapy vs, dutasteride monotherapy in the presence of these significant baseline parameters remained relatively unchanged (relative risk: 3.41, 95% CI: 1.12, 10.38).

As in REDUCE, there were no differences among treatment groups in the incidence of events that may trigger cardiac failure such as myocardial infarction, myocardial ischemia, atrial fibrillation, or other arrhythmias.

7.8.2.3. Additional Analyses Related to Cardiovascular Safety

MACE

Post-hoc analyses of Major Adverse Cardiovascular Events (MACE) were conducted for REDUCE and CombAT. MACE was defined as a composite of Cardiovascular Death, Non-fatal myocardial infarction (MI), and Stroke, where “Cardiovascular Death” is defined as any fatal AE in the Cardiac Disorders System Organ Class (SOC) plus the preferred term of Sudden Death (General Disorders SOC), “Non-fatal MI" is defined as any non-fatal event coded to one of the "narrow" preferred terms in the MedDRA SMQ "Myocardial infarction,” and "Stroke" is defined as any event (fatal or non-fatal) coded to one of the "narrow" preferred terms in the MedDRA SMQ "Central nervous system haemorrhages and cerebrovascular conditions."

No significant differences in proportions of subjects with MACE were seen in REDUCE (Table 60) or CombAT (Table 61).

Table 60 Number (%) of Subjects with Major Adverse Cardiovascular Events (MACE) (REDUCE Safety Population)

Event	Placebo n (%) N=4126	Dutasteride n (%) N=4105	Relative Risk Estimate[a]
Any Major Adverse CV Event (MACE)	130 (3.2)	134 (3.3)	1.04 (0.82, 1.32)
Cardiovascular death	25 (0.6)	26 (0.6)	
Non-fatal myocardial infarction	48 (1.2)	47 (1.1)	
Stroke	60 (1.5)	67 (1.6)	

a Relative risk (hazard ratio) vs. Placebo based on Cox proportional hazards model

Table 61 Number (%) of Subjects with Major Adverse Cardiovascular Events (MACE) (CombAT ITT Population)

Event	Dut + Tam (N=1610) n (%)	Dutasteride (N=1623) n (%)	Tamsulosin (N=1611) n (%)
Any Major Adverse CV Event (MACE)	63 (3.9)	67 (4.1)	56 (3.5)
Cardiovascular death	16 (1.0)	12 (0.7)	14 (0.9)
Non-fatal myocardial infarction	20 (1.2)	24 (1.5)	15 (0.9)
Stroke	28 (1.7)	32 (2.0)	28 (1.7)

Dut=dutasteride; Tam=tamsulosin

Relative risk (hazard ratio) estimates (95% CI) for any MACE were 0.95 (0.67, 1.34) for combination vs. dutasteride and 1.10 (0.77, 1.57) for combination vs. tamsulosin.

Integrated Analyses

Data from REDUCE and CombAT were integrated with pooled Phase III BPH trials of dutasteride monotherapy in order to analyze the composite event of cardiac failure across the dutasteride program. The use of alpha blockers was not permitted in these studies. The pooled dataset from the BPH trials contains data from 4325 men randomized to treatment with dutasteride (n=2167) or placebo (n=2158). These studies were 4 years in duration; the first 2 years of these trials were double-blind and placebo-controlled, followed by another 2 years of an open-label phase. Of the 4325 subjects randomized to dutasteride or placebo in the double-blind phase, 2340 enrolled in the open-label phase and 1667 subjects completed the open-label phase. Demographic and baseline characteristics were similar across treatment groups. Subjects were predominantly White (91%-92%), with a median age at baseline of 66 years in the placebo group (range, 47-91 years) and 67 years in the dutasteride group (range, 50-94 years). Thirteen percent (13%) of subjects in each group were smokers.

Ninety percent (90%) of subjects in the placebo group and 88% of subjects in the dutasteride group reported one or more current medical conditions at baseline, and patterns of current medical conditions were generally similar between the treatment groups. The most common current medical conditions were associated with the cardiovascular (47% each treatment group), musculoskeletal (39% placebo group, 41% dutasteride group), and endocrine and metabolic (30% placebo group, 29% dutasteride group) systems.

The integrated analyses were done in two ways.

The first analysis integrated data from placebo-controlled trials. Complete data from REDUCE were integrated with Year 2 data from the phase III BPH studies, where there is a dutasteride vs. placebo comparison. From this integrated analysis, the proportion of subjects with cardiac failure was 0.7% in both groups (44/6284 in the placebo group and 43/6272 in the dutasteride group). The relative risk estimate for dutasteride vs. placebo was 0.99 (95% CI: 0.65, 1.50). Kaplan-Meier analysis of time to first cardiac failure event for these integrated studies showed similar rates of cardiac failure events by treatment group over the duration of the studies.

The second analysis integrated data from REDUCE, CombAT, and the pooled Phase III BPH trials up to Year 4, adding in events experienced by dutasteride subjects in the open-label phase after they had double-blind placebo treatment. This analysis therefore represents all composite cardiac failure events across all of the 4-year dutasteride studies. From this integrated analysis, the proportion of subjects with cardiac failure is 0.7% in the placebo and dutasteride groups (44/6284 and 61/9047, respectively). The relative risk estimate for dutasteride vs. placebo is 0.96 (95% CI: 0.65, 1.41). Kaplan-Meier analysis of time to first cardiac failure event for these integrated studies showed similar rates of cardiac failure events in the dutasteride and placebo groups over 4 years.

7.8.2.4. Summary

In the REDUCE trial in men at increased risk of prostate cancer, there was a higher incidence of the composite event ‘cardiac failure’ in the dutasteride group (30/4105, 0.7%) compared to the placebo group (16/4126, 0.4%). In a *post-hoc* analysis of concomitant alpha blocker use, there was a higher incidence of the composite event ‘cardiac failure’ in subjects taking dutasteride and an alpha blocker concomitantly compared with subjects taking dutasteride and no alpha blocker, placebo and an alpha blocker, or placebo and no alpha blocker.

In the CombAT trial in men with BPH, there was a higher incidence of the composite event ‘cardiac failure’ in the dutasteride + tamsulosin combination therapy group (0.9%) compared to the dutasteride monotherapy group (0.2%) and the tamsulosin monotherapy group (0.6%).

Across the dutasteride clinical trial program, rates of the composite event ‘cardiac failure,’ are variable between studies and lower than expected for a population of older men with a high rate of cardiovascular conditions at baseline. Men with BPH and lower urinary tract symptoms (LUTS) have a high prevalence of cardiovascular disease as their age and co-morbidities put them at increased risk [Souverein, 2001] observed that chronic diseases and indicators of cardiovascular disease were more prevalent among patients starting drug treatment for BPH compared to age-matched controls not prescribed BPH therapy [Michel, 2004] examined baseline data in 9857 men seeking treatment for BPH symptoms and noted the extent of BPH symptoms was significantly greater in patients with hypertension, and that each 1 point increase in International Prostate Symptom Score (IPSS) significantly increased the risk of being hypertensive. Although BPH and hypertension appear to involve separate disease processes, it has been

postulated that age-related increases in sympathetic tone may play a role in their pathophysiologies [Boyle, 1995].

Men in REDUCE and CombAT shared similarly high rates of reported cardiovascular co-morbidities to those seen in BPH epidemiological studies [Roehrborn, 2007; Hutchison, 2006, Rosen, 2003], as well as high rates of concomitant cardiovascular medication use that would place them already at baseline at an increased risk of experiencing cardiovascular events and cardiac failure.

Although not specific to men with BPH or prostate cancer, data from the Framingham Heart Study (FHS) and the Atherosclerosis Risk in Communities (ARIC) Cohort Study for men age 55-74 years provide some context for evaluating the rates of cardiovascular events in dutasteride clinical trials [National Institutes of Health, 2006]. Although direct comparisons are not possible, the rates of cardiovascular events in dutasteride clinical trials are generally consistent with the rates in these large epidemiological studies.

Notably, the incidences of cardiac failure with dutasteride monotherapy were comparable in REDUCE (0.7%) and the pooled Phase III BPH monotherapy trials (0.6% at Year 2), while the incidence in the REDUCE placebo group (0.4%) was lower than in the Phase III BPH placebo group (1.3%). In CombAT, rates of cardiac failure events in all treatment groups (0.2% to 0.9%) were low compared to Year 2 rates in the placebo group (1.3%) of the pooled Phase III BPH studies. Differences among treatment groups in the incidence of other cardiovascular events that might trigger cardiac failure (e.g., myocardial infarction, coronary artery disease, arrhythmias) were not seen. Finally, the high prevalence of pre-existing cardiovascular conditions and high use of medications with potential effects on blood pressure and cardiac function contribute to the difficulty in evaluating the findings with respect to cardiac failure events in these studies. It is important to note that none of the dutasteride clinical trials were designed as cardiovascular outcomes studies; cardiovascular AEs were not collected in a targeted manner or adjudicated, and there were no attempts to control prospectively for cardiovascular risk factors.

The etiology of the imbalances in events of cardiac failure observed in REDUCE and CombAT is unknown. One possible explanation for this imbalance is an unknown pharmacokinetic or pharmacodynamic interaction between dutasteride and alpha blocking agents; however, a causal relationship cannot be determined based on the available data. Mechanistically, it is unclear how dutasteride and alpha blockers in combination would be associated with a risk of cardiac failure. No pharmacokinetic or pharmacodynamic interactions between dutasteride and tamsulosin or terazosin were observed in a Phase 1 drug interaction study (ARIA1011), a randomized, open-label, 56-day crossover study in 48 healthy volunteers.

- The cardiac failure data from REDUCE and CombAT have been reviewed by the Division of Urological Drug Products (DRUDP) of the FDA. DRUDP reviewed and adjudicated all cases counted toward the composite term of cardiac failure in both trials, and consulted with other divisions within the agency, including the Cardio-renal Division, Office of Oncology Drug Products, and Office of Surveillance and Epidemiology. Following this review, FDA notified GSK that several cases did not

fit the clinical scenario for cardiac failure. FDA's count of subjects with cardiac failure events in REDUCE was 26/4105 (0.6%) in the dutasteride group and 15/4126 (0.4%) in the placebo group. FDA's count of subjects with cardiac failure events in CombAT was 12/1610 (0.7%) in the combination group, 2/1623 (0.1%) in the dutasteride monotherapy group, and 9/1611 (0.6%) in the tamsulosin monotherapy group. FDA concluded that no causal relationship between cardiac failure and dutasteride use has been established. The incidence of cardiac failure in REDUCE and CombAT is described in the "Adverse Reactions" section of the Prescribing Information for AVODART.

- In conclusion, there is no clear biological explanation for the cardiac failure findings in REDUCE and CombAT. Careful review of the cases by both GSK and FDA has shown that some events reported as 'cardiac failure' were clearly not congestive heart failure. The majority of cases occurred in subjects with concomitant medical conditions that put them at increased risk of cardiac failure events.

7.9. Laboratory Data, Vial Signs and Other Safety Measures

7.9.1. Laboratory Parameters

7.9.1.1. Transitions in Laboratory Parameters

In REDUCE, the majority of the of subjects in each treatment group had laboratory parameters (hematology and clinical chemistry) that remained within normal range from baseline to the final assessment and experienced no changes from baseline categories (low, normal, high) (Appendix F Table 78 and Table 79). No clinically significant changes in laboratory data, vital signs or other safety measures were seen. These observations were also noted for the dutasteride monotherapy in CombAT.

This is consistent with previous studies in subjects taking 0.5 mg dutasteride.

Individual Subject Liver Function Test Values of Clinical Concern

Two subjects had elevations of alanine aminotransferase (ALT) and bilirubin across these studies. One subject (Subject 53490) was in the tamsulosin monotherapy group of CombAT and experienced the onset of severe abdominal pain, metastases to liver, and pancreatic neoplasm which were not drug-related in the investigator's assessment, led to discontinuation of study drug and eventually had a fatal outcome.

The second subject (Subject 51058) was in the dutasteride monotherapy group of CombAT and had elevations above the normal range, for aspartate aminotransferase (AST), ALT and total bilirubin concentrations 6 days after commencing treatment with ezetimibe for the treatment of high cholesterol in addition to atorvastatin. Ezetimibe treatment was stopped approximately 1 week after the report of ALT, AST, and total bilirubin elevations, whereas the investigational product and atorvastatin were continued. At the subsequent Month 24 visit, the ALT, AST, and total bilirubin levels had returned to normal and subsequently remained constant for the duration of the study.

Due to confounding medications/comorbid conditions, GSK considers it likely that have been due to alternative causes other than drug induced hepatotoxicity.

7.9.1.2. Threshold Laboratory Values

At baseline the percentage of subjects with any laboratory parameter outside pre-specified threshold values was low and similar between the treatment groups. Multipliers used to determine threshold values are shown in Appendix F Table 77. The percentage of subjects with any post-baseline laboratory parameter outside pre-specified threshold values was low and similar for the two treatment groups (5%). The most frequently reported clinical chemistry parameter outside pre-specified threshold values was elevated glucose occurring in 3 % of subjects in each treatment group; for all other analytes reports of outside pre-specified threshold values were <1%. Mean values and change from baseline, for all laboratory parameters were similar in treatment groups at baseline and Months 12, 24, 36, 48, and final visit assessments. Results from REDUCE and CombAT were consistent with one another.

In REDUCE, a similar percentage of subjects aged ≥65 years had post-baseline threshold laboratory values compared with subjects aged <65 years (5% to 6%). In CombAT, more subjects aged ≥65 years in the dutasteride monotherapy group had post-baseline threshold laboratory values compared with subjects aged <65 years (5% vs 2%, respectively).

- Over time, there were no differences in mean values at baseline and subsequent assessments of all laboratory parameters for the dutasteride monotherapy groups from both studies.

7.9.2. Vital Signs

Mean baseline values for blood pressure and heart rate were similar for the dutasteride and placebo groups and there were no notable changes in mean values over time. The proportion of subjects with baseline vital signs outside threshold limits was similar between treatments. Threshold ranges are shown in Appendix F Table 80). The percentage of subjects with post-baseline vital signs outside threshold limits was low, though significantly greater in the dutasteride group than the placebo group (14% vs. 12%, respectively; p=0.0052). Post-baseline changes were noted in both systolic and diastolic blood pressure, as well as heart rate. The most frequently reported threshold value in each treatment group was elevated systolic blood pressure (Table 62).

Table 62 Subjects with Any Post-baseline Threshold Vital Sign Measurement (REDUCE Safety Population)

	Placebo N= 4126 n/N[a] (%)		Dutasteride N= 4105 n/N[a] (%)	
	Baseline	Post-baseline	Baseline	Post-baseline
Any threshold value	225/3879 (6)	453/3922 (12)	192 /3854 (5)	532/3893 (14)
Systolic blood pressure				
<80 mmHg	0/3895	0/3922	0/3871	2/3897 (<1)
>165 mmHg	196/3895 (5)	392/3922 (10)	166/3871 (4)	442/3897 (11)
Either threshold	196/3895 (5)	392/3922 (10)	166/3871 (4)	444/3897 (11)
Diastolic blood pressure				
<40 mmHg	0/3895	0/3922	0/3871	0/3897
>105 mmHg	44/3895 (1)	100/3922 (3)	38/3871 (<1)	105/3897 (3)
Either threshold	44/3895 (1)	100/3922 (3)	38/3871 (<1)	105/3897 (3)
Heart rate				
<40 beats/min	0/3878	3/3922 (<1)	0/3857	1/3893 (<1)
>100 beats/min	17/3878 (<1)	56/3922 (1)	15/3857 (<1)	79/3893 (2)
Either threshold	17/3878 (<1)	59/3922 (2)	15/3857 (<1)	80/3893 (2)

a. n/N =number of subjects with a threshold value/ number of subjects evaluated for the parameter

In CombAT, a higher percentage of subjects in the dutasteride monotherapy group had post-baseline threshold vital signs changes compared with the dutasteride group in REDUCE. This difference could be partly explained by the different population characteristics and the reported association between BPH and hypertension. In addition, vital signs were assessed more frequently in CombAT, increasing the likelihood of an abnormal value being detected in CombAT. The percentages of subjects reporting hypertension as an AE are similar among all treatment groups in the two studies for overall AEs and AEs by age.

Baseline height and weight were collected for all subjects and body mass index (BMI) was computed from these values. Mean BMI values at baseline and Month 48 were similar across the treatment groups in REDUCE (Table 63). Changes from baseline in BMI were small and similar between the treatment groups.

Table 63 BMI Change from Baseline (REDUCE Safety Population)

BMI	Placebo N=4126	Dutasteride N=4105
Baseline, n	n=4057	n=4027
Mean (SD)	27.4 (4.20)	27.4 (3.89)
Month 48, n	n=2369	n=2449
Mean (SD)	27.6 (4.06)	27.7 (3.98)
Change from Baseline to final assessment, n	n=3201	n=3191
Mean (SD)	0.1 (2.38)	0.3 (2.37)

7.9.3. Gynecomastia Evaluation

No clinically relevant trends were noted in gynecomastia examinations. At baseline, 7% to 8% of subjects in the placebo and dutasteride treatment group, respectively, of

REDUCE had palpable breast tissue and <1% in each treatment group had nipple tenderness; few of these findings were regarded as clinically significant.

Post-baseline, the percentage of subjects who developed palpable breast tissue was 2% higher in the dutasteride group (11%) relative to placebo (9%). Of the subjects with either palpable breast tissue or nipple tenderness, most findings were not regarded as clinically significant. However, the subjects in the dutasteride groups had a greater percentage of clinically significant findings for palpable breast tissue relative to placebo (13% vs. 8%, respectively).

REDUCE and CombAT dutasteride monotherapy groups showed gynecomastia findings that were consistent with one another.

7.9.4. Digital Rectal Examination

The baseline DRE for subjects in REDUCE indicated prostate abnormalities for a small percentage of subjects in each treatment group (4% for placebo and dutasteride groups), and the majority of these were not considered clinically significant.

In each treatment group, 6% of subjects had changes from normal to abnormal and of these, 29% and 33% were clinically significant in the placebo group and dutasteride group, respectively. A biopsy was recommended for the majority of subjects with a clinically significant abnormality.

Baseline and post-baseline prostate abnormalities were similar in the dutasteride group of REDUCE and the dutasteride monotherapy group of CombAT. The percentages of clinically significant prostate abnormalities detected by post-baseline DRE were 33% and 42% of the abnormal prostates in the dutasteride group of REDUCE and the dutasteride monotherapy group of CombAT, respectively.

7.10. AEs by Age, Race and Medical Conditions

Age had no clinically meaningful effect on the safety and tolerability of dutasteride.

The majority of subjects in REDUCE and CombAT were White (87% to 91%), making it difficult to interpret data regarding differences in rates of AEs in racial subgroups. The overall percentage of subjects reporting AEs was higher in the Non-White population compared with the White population, although, as noted, the Non-White population was small and comprised of subgroups including Black, Asian, and American Hispanic.

Current cardiovascular conditions (including hypertension) and metabolic conditions were common in this subject population. Forty-eight percent of subjects in each treatment group in REDUCE reported at least one current cardiovascular medical condition. The distribution of AEs by treatment group was similar for subjects with and without current cardiovascular disease, with more AEs of erectile dysfunction and libido decreased among dutasteride-treated subjects. As expected, more subjects in the subgroup with current cardiovascular disease reported cardiac disorders compared to those in the subgroup without cardiovascular disease. Results from the dutasteride

monotherapy group in CombAT were similar to results in the dutasteride group in REDUCE.

Twenty percent of subjects in each treatment group in REDUCE gave an affirmative response when asked if they had diabetes, glucose intolerance or other current endocrine and metabolic conditions. The overall AE profile was similar among subjects with and without current endocrine or metabolic conditions. However, a higher percentage of subjects within the SOC 'Metabolism and nutrition disorders' was noted for subjects with endocrine/metabolic disorders, as expected, and a higher incidence was observed for the 'Cardiac disorders' SOC for subjects reporting current endocrine or metabolic conditions. Similar to results for the Safety population as a whole, more dutasteride-treated subjects than placebo-treated subjects in both subgroups reported AEs of erectile dysfunction and libido decreased. Results from the dutasteride monotherapy group in CombAT were similar to results in the dutasteride group in REDUCE.

7.11. Drug Interactions

AE data from REDUCE reveal no treatment group-dependent evidence of clinically significant drug-drug interactions between study therapy and drugs commonly used in the men enrolled in the studies. The majority of subjects in the study (93% to 94%) used one or more concomitant medications at some point during the study. AEs were summarized by the use (yes/no) of selected concomitant medications at any time after randomization. AEs were assessed by concurrent use of cardiovascular drugs (ACE inhibitors, beta blockers, calcium antagonists, and diuretics), endocrine and metabolic drugs (anti-hyperlipidemics and corticosteroids), NSAIDs, salicylates, phosphodiesterase Type V inhibitors (i.e., sildenafil and sildenafil citrate), and 4-quinolones.

The overall percentages of subjects with AEs were higher for subjects using each type of current medication compared with non-users, with most of these AEs representing the most common AEs seen in the studies (e.g., nasopharyngitis, back pain, URTI). As expected, the percentages of subjects with AEs that would be associated with the use of a particular concurrent medication were also higher for users than non-users (e.g., higher percentage of subjects with musculoskeletal pain among NSAID users than non-users and higher percentage of subjects with prostatis among quinolone users compared to non-users).

In REDUCE, among subjects not taking each of the medications, slightly more subjects in the dutasteride monotherapy group experienced AEs relative to the placebo group. Dutasteride monotherapy-treated subjects taking calcium antagonists reported a higher percentage of AEs relative to placebo-treated subjects than did dutasteride monotherapy-treated subjects not taking calcium antagonists.

The incidence rate of cardiac disorders was also analyzed per treatment group for subjects taking selected concomitant medications. In REDUCE, there were more 'Cardiac disorder' AEs in both treatment groups among subjects taking the medications when compared with subjects not taking the medications. Within the group of subjects who used the medications, slightly more placebo-treated than dutasteride monotherapy-treated subjects experienced 'Cardiac disorder' AEs. Among subjects not taking each of

the medications, the percentages of subjects with 'Cardiac disorder' AEs were similar between the treatment groups.

In CombAT, the evaluation of cardiac disorders in dutasteride monotherapy subjects taking selected concomitant medications also did not reveal drug-drug interactions that impacted AE incidence. No treatment group-dependent pattern of increased percentage of subjects with cardiac disorders was observed.

7.12. AEs Reported After Treatment Stopped

The percentage of subjects reporting AEs after treatment stopped was higher in the placebo-treated subjects (14%) compared with dutasteride-treated subjects (11%), but low overall in REDUCE. There were no notable differences in the percentage of subjects reporting AEs across the two treatment groups and all individual AE preferred terms reported by <1% of subjects, with the exception of erectile dysfunction in placebo-treated subjects (1%).

7.13. SAEs Reported in the 120-Day Safety Update

The 120-day safety update contained safety data from REDUCE that were collected from 01-Dec-2009 to 30-Apr-2010. There were no new SAEs and 2 follow-ups to previously-reported SAEs (osteoarthritis and tendon rupture) during the update period. The follow-up information provided clarification on surgical treatment of the SAEs and event dates. There were no deaths reported during the update period.

The update also contained safety data from CombAT that were collected from 21-Aug-2009 to 30-Apr-2010. There were no new SAEs and 1 follow-up to a previously reported SAE (reported event was changed from "chest x-ray abnormal" to "gastritis" during the update period. There were no deaths reported during the update period.

In ARI103094, new SAEs and 2 new deaths were reported (see Section 8.5).

7.14. Post-Marketing Experience

7.14.1. Exposure

Dutasteride has been on the market in the US since January 2003 and is available in the EU and many international markets for treatment of BPH. Approximately 5.5 million person-years of treatment have been sold world-wide, based on sales data (IMS Health, June 2010) and assuming a total daily dose of 0.5 mg.

7.14.2. Overview of Spontaneous Reports

GSK enters all spontaneous reports of adverse events associated with dutasteride into a worldwide database, OCEANS. This database facilitates GSK's proactive process for identifying safety signals for marketed products, which has three main components: (1) regular, systematic review of aggregate safety data, including trend analysis to detect

increased frequency of reporting; (2) timely awareness and review of important individual cases; and (3) regular review of the literature.

From the launch of dutasteride in January 2003 through 30 April 2010, GSK received 5582 spontaneous reports containing 10,977 adverse events for dutasteride. Approximately 58% of these reports came from the US.

The dutasteride product label contains most of the commonly reported events (Table 64): sexual events (including decreased semen volume), breast disorders, and events consistent with allergic reactions. Exceptions are pollakiuria and dysuria (likely BPH-related) and the non-specific events dizziness, fatigue, headache, and diarrhea. A review of reports of alopecia and other disorders of hair growth was recently reviewed by FDA; no changes to labeling changes were warranted.

Table 64 Most Common (>100 Reports) Spontaneously Reported Adverse Events (GSK OCEANS Database, 30 April 2010)

Event (MedDRA Preferred Term)	Number of Events
Gynaecomastia	345
Erectile dysfunction	306
Libido decreased	208
Rash	207
Breast tenderness	199
Dizziness	198
Dysuria	181
Breast enlargement	171
Pollakiuria	168
Pruritus	135
Breast pain	124
Fatigue	109
Alopecia	106
Headache	105
Diarrhea	103
Semen volume decreased	102

7.14.3. Events of Interest

GSK monitors post-marketing reports of cardiovascular adverse events, breast cancer events, high-grade prostate cancer, and pregnancy outcomes as events of special interest for dutasteride. Recent reviews of these events are summarized below. Recognizing the limitations of spontaneous data (under-reporting, incomplete data, and unknown drug exposure), these reviews provide descriptive information only.

7.14.3.1. Cardiovascular Events

Review of the published medical literature has identified no reports of cardiac failure associated with dutasteride given alone or in combination with an alpha blocker.

The GSK worldwide safety database was searched for spontaneous reports and post-marketing surveillance reports within the MedDRA High Level Group Term (HLGT)

'Heart Failure' where dutasteride was reported as a suspect or concomitant drug. All MedDRA Preferred Terms with primary or secondary mapping to the HLGT 'Heart Failure' were included. Of note, events consistent with peripheral edema were captured in this search. As of 30 April 2010, GSK had received a total of 81 such cases:

- 37 cases (46%) were reported by a consumer; 37 cases (46%) were reported by a physician.
- 79 cases (98%) described male patients, with an age range of 57 to 91 years.
- 32 cases (40%) met the criteria for a serious adverse event report.
- 28 cases (35%) reported use of an alpha blocker, primarily tamsulosin, as a concomitant medication.
- 71 (88%) of the 81 cases were captured in the search due to events of peripheral or localized edema (69 cases), peripheral edema and pericardial effusion (1 case), and pulmonary congestion (1 case). In more than half of these cases, peripheral or localized edema, often of the hands or fingers, appeared to be consistent with hypersensitivity reactions, injury, infection, or other diagnoses. The remaining cases described primarily lower limb edema, in some cases with weight gain. Time to onset of lower limb edema, where described, ranged from 1 day to 6 months. Several cases described edema in patients with pre-existing cardiac disease or heart failure.
- 10 (12%) of the 81 cases, all serious, described events of cardiac failure:
    - Three cases listed rosiglitazone as the suspect drug and dutasteride as a concomitant medication. None of these cases included information on the temporal relationship between the events and use of dutasteride.
    - Three cases described heart failure events with onset ≥1 year after the last dose of dutasteride in REDUCE and were reported in ARI103094, an observational follow-up study to REDUCE. No subject was taking dutasteride at the time of the events. All 3 subjects had a history of cardiac disease, and heart failure was associated with atrial fibrillation.
    - The remaining 4 cases are summarized in Table 65.

Table 65 Spontaneous Reports of Cardiac Failure

Case ID	Age (yrs)	Serious Events	Suspect Drugs (Concomitant Drugs)	Time to Onset	Action Taken with Suspect Drug	Hospitalization/ Outcome	Relevant Medical History
A0579784A	NR	Congestive heart failure (and non-serious fluid retention[a])	Dutasteride	NR	Discontinued	Unknown/ Unknown	NR
A0667335A	68	Congestive heart failure	Dutasteride (Tamsulosin, many others)	"months"	None	Yes/ Unresolved	COPD Emphysema
A0760916A	80	Cardiac insufficiency, Cardiomegaly	Dutasteride (Aspirin, Doxazosin)	~1month	None	Unknown/ Death	Hypertension Obesity Tobacco use
B0628408A	81	Aggravated cardiac failure	Dutasteride (Silodosin)	NR	NR	Unknown/ Unknown	Cardiac failure

COPD=chronic obstructive pulmonary disease, HGLT= MedDRA High Level Group Term, Met=metformin, N/A=not applicable, NR= not reported

a. Reporting cardiologist stated that fluid retention is attributed to dutasteride; urologist stated that the patient may have already had fluid retention which led to heart failure.

7.14.3.2. High-Grade Prostate Cancers

As of 30 April 2010, GSK had received 19 spontaneous reports of prostate cancer in men taking dutasteride. Two of the 19 reports described suspicion of prostate cancer without a diagnosis. In most cases, the temporal relationship between use of dutasteride and diagnosis of prostate cancer was not provided. Where reported, time to onset of prostate cancer ranged from several weeks to 3 years after starting treatment with dutasteride. In 2 cases, prostate cancer was detected prior to starting treatment with dutasteride. In 7 cases, increased prostate-specific antigen (PSA) was also reported as an adverse event.

Six of the 19 reports of prostate cancer included the Gleason score. Gleason scores were 6 (1 case), 8 (1 case), 9 (3 cases), and "high-grade neoplasm with Gleason score 7-10" (1 case). Cases with Gleason scores of 7 or higher are described below:

- The "high-grade neoplasm with Gleason score 7-10" was diagnosed in an 81-year-old man who received dutasteride over a period of 2 years. The patient's PSA value was reported as "severely increased." Dutasteride was discontinued and the patient was treated with gonadotropin releasing hormone analogue. Prostate cancer was unresolved at the time of reporting.
- The Gleason score 8 cancer was diagnosed 5 months after starting dutasteride in a man of unreported age who had a history of a negative prostate biopsy. Increased PSA was reported as a concomitant condition. Treatment and outcome were not reported.

- One Gleason score 9 cancer was diagnosed approximately 1 year after starting dutasteride in a 69-year-old man with pre-existing prostatic adenoma treated for several years with finasteride. After 9 months on dutasteride, palpatory exam revealed a new nodule in the prostate. Rising PSA was noted 11 months after starting dutasteride. Dutasteride was discontinued and the patient was treated with goserelin acetate. Radiotherapy was initiated following detection of lymph node metastases. The events were not resolved at the time of reporting.
- One Gleason score 9 cancer was diagnosed approximately one month after starting dutasteride treatment in an 80-year-old man. Increasing PSA was also reported as an adverse event. Dutasteride was discontinued. The patient was treated with hormonal suppression with some improvement of PSA values. Prostate cancer was reported as unresolved.
- One Gleason score 9 cancer was diagnosed approximately 1 month after starting dutasteride treatment in a 73-year-old man with a history of lung cancer. Treatment and outcome were not reported. This case was reported by a consumer and not confirmed by a physician.

7.14.3.3. Male Breast Cancer

As of 30 April 2010, GSK had received 12 spontaneous reports of male breast cancer in men taking dutasteride. Two additional spontaneous reports have been received since that date, bringing the total to 14 spontaneous reports. These 14 spontaneous reports are in addition to 2 reports of breast cancer in men taking dutasteride in the pivotal BPH trials (ARIA3002 and ARIB3003). Based on these 16 reports and the estimated cumulative exposure, the crude incidence of male breast cancer in dutasteride-exposed men is 0.29 per 100,000 person-years (16/5,500,000 x 100,000). This crude rate is lower than the age-adjusted male breast cancer incidence of 1.27 per 100,000 persons from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute (US) for 2006 [Horner, 2009].

In the 16 cases of male breast cancer reported to GSK, median patient age was 73.5 years (mean, 72 years; range, 62 to 81 years). Median time to onset, or time to diagnosis, was 8.5 months (range, 10 weeks to 2 years) after starting dutasteride therapy. Five reports specified the type of cancer: ductal carcinoma (4 cases) and papillary carcinoma (1 case). Relevant medical history was noted in 6 cases and included at least one known risk factor for breast cancer (3 cases), a previous diagnosis of another type of cancer (2 cases), and a concurrent medication (one case).

No reports of breast cancer in persons taking dutasteride have been identified in the literature; however, a report of an *in vitro* study of dutasteride and breast cancer has been published [Wiebe, 2006]. This study investigated the effects of dutasteride on tumorigenic and non-tumorigenic breast cell lines. Type 1 5α-reductase is the predominant isoenzyme in breast tissue and breast cell lines. Studies have shown that breast cancer tissue and cell lines have higher 5α-reductase levels than normal breast tissue or non-tumorigenic cell lines, and that 5α-reduced progesterone metabolites promote mitogenic and metastatic activity in breast cell lines. In this study, dutasteride inhibited progesterone conversion to 5α-reduced progesterone metabolites by >95% and

increased 4-pregnene production, resulting in inhibition of breast cell proliferation and detachment. The authors conclude that these findings suggest that dutasteride may have the potential to suppress mammary cell tumor formation and/or growth.

7.14.3.4. Pregnancy Outcomes

GSK seeks follow-up information on all reports of exposure to dutasteride during pregnancy, due the potential for dutasteride to interfere with the formation of external genitalia in the male fetus.

As of April 2010, GSK had received 103 spontaneous reports describing exposure of pregnant women to dutasteride. Most of the reports described exposure via contact of the capsule or capsule contents with the skin or via semen in women who were pregnant or became pregnant while their male partners were taking dutasteride. One report described accidental oral ingestion of a single dose of dutasteride by a pregnant woman. In 2 additional reports, the route of exposure was not clearly described.

Pregnancy outcomes are available for 14 of the 103 cases and include 10 live births with no apparent congenital anomalies, 1 elective pregnancy termination with no apparent congenital anomaly, and 3 abnormal outcomes, as summarized below:

- 1 infant with tracheoesophageal fistula, club foot, and knee deformity who died shortly after birth. The mother was a nurse who handled dutasteride over a period of 3 years prior to conception.

- 1 infant with hypospadias and cryptorchism born to a woman exposed to dutasteride at 8 weeks gestation by handling dutasteride capsules, as well as feces and urine, while caring for a man with BPH.

- 1 report of spontaneous abortion at approximately 6 weeks gestation in a woman exposed to dutasteride via her partner who was taking dutasteride.

Pregnancy outcomes are unknown in the remaining 89 cases, one of which stated that possible feminization of the fetus was suspected at 11 weeks gestation.

7.14.4. Summary

The post-marketing safety profile of dutasteride is generally consistent with the safety profile established in clinical trials. Since the launch of dutasteride, regular reviews of post-marketing safety data and the literature have resulted in the addition of “allergic reactions” to the Adverse Reactions section of the labeling and amendment of the dosage and administration section to state that contact with the contents of the dutasteride capsule may result in irritation of the oropharyngeal mucosa. Amendments to the Adverse Reactions section of the labeling are in progress to add information on reports of breast cancer in clinical trials and in post-marketing experience.

No other safety concerns warranting labeling changes or important information regarding drug interactions, overdose, or abuse potential have been identified through routine review of post-marketing data.

7.15. Safety Conclusions

This Briefing Document has reviewed the safety data from the pivotal study REDUCE, which investigated the use of dutasteride for 4 years to reduce the risk of prostate cancer in men at increased risk of the disease, and the supportive safety study CombAT, which investigated the use of dutasteride alone and in combination with tamsulosin for 4 years for treatment of BPH. A total of 7338 subjects were treated with dutasteride 0.5 mg once daily for up to 4 years in the two studies, either as monotherapy (5728 subjects) or in combination with 0.4 mg tamsulosin (1610 subjects). Safety data from the two studies are central to the overall safety evaluation plan in this submission.

The results from these 4-year studies support the following conclusions regarding the use of dutasteride for reducing the risk of prostate cancer in men at increased risk of developing the disease:

- The safety profile of dutasteride in men at increased risk of prostate cancer is generally consistent with the well-established safety profile in men with symptomatic BPH, as described in the current product labeling, with the exceptions of the imbalance seen in reported cases of cardiac failure (Section 7.8.2) and the numerical difference in Gleason score 8-10 prostate cancers (Section 3.2.1).
- With the exception of erectile dysfunction, similar percentages of subjects in the dutasteride and placebo groups reported the most common AEs.
- In REDUCE and CombAT, the incidence of cardiac failure was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects on dutasteride alone. The percentages of subjects experiencing a cardiac failure event were low (≤1%) and variable among the studies. The etiology of this finding is unclear, as there was no associated increase in overall cardiovascular events, or cardiac events that often precipitate heart failure (e.g. cardiac arrhythmias, coronary artery disease), and no imbalance in adverse events seen with cardiac failure (e.g. orthopnea, edema, dyspnea). The overall low number of subjects experiencing these AEs, the prevalence of pre-existing cardiovascular conditions in this study population, and the use of medications with potential effects on blood pressure and cardiac function make the evaluation of the observed imbalance in reported AEs of cardiac failure (composite) difficult to interpret. These findings are described in the "Adverse Reactions" section of the AVODART label, though no causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established.
- In REDUCE, as presented in Section 3.2.1, the incidence of Gleason score 7 to 10 cancers in both treatment groups was similar overall and by study periods. However, in Years 3 to 4, there were more subjects with Gleason score 8 to 10 cancers in the dutasteride monotherapy group in comparison with placebo. As presented in Section 3.3, prostate cancer data from CombAT, in which biopsies were only

performed for cause, showed lower proportions of subjects with prostate cancer across all Gleason score categories in the dutasteride-containing treatment groups as compared to tamsulosin monotherapy. There was no difference in the proportions of subjects with high grade Gleason score 8-10 cancers between the dutasteride monotherapy group and the tamsulosin monotherapy group during Years 3-4. As presented in Section 5.4.2.1, data from the REDEEM trial showed that similar percentages of subjects in the dutasteride and placebo treatment groups had higher Gleason scores on final biopsy compared to baseline biopsy.

8. ARI103094 – ONGOING STUDY

8.1. Narrative Description of Study

Study ARI103094 is an ongoing international, multicenter, 2 year observational follow-up study of men who participated in REDUCE. The study is designed to collect ongoing prostate cancer information (Part A, 2 Year Observational Study) and/or to collect positive biopsy tissue obtained during the REDUCE study period, for future biomarker research (Part B, Prostate Biopsy Tissue Study). A secondary objective was to collect and summarize data on SAEs for 2 years beyond the 4 year prospectively planned 4 year double-blind, placebo-controlled REDUCE study.

Part A is an observational study in which subjects are followed for 2 years after they have completed the REDUCE 4 Year Contact which is either the REDUCE 4 Year study visit or the 4 Year phone call for withdrawn subjects in follow-up.

Eligible subjects for Part A had participated in REDUCE and a) completed 4 years on study drug through Visit 10, or b) were diagnosed with prostate cancer during REDUCE, discontinued study drug, but participated in modified assessments and procedures through the 4 year anniversary of their randomization date or c) withdrew from REDUCE study drug and study visit participation, but participated in phone call follow-ups every 6 months through the 4 year anniversary of their randomization date.

Subjects were eligible for Part B if they were diagnosed with prostate cancer based on a prostate biopsy during participation in REDUCE. Because of the small number of subjects who were eligible and/or consented to Part B of the study it was felt that no meaningful scientific information would be gleaned and therefore it was decided to cancel Part B.

Subject recruitment occurred from April 2009 through 31 December 2009. As of 04 February 2010, the clinical cut-off date for subjects who had completed Year 2 of this study, 2795 subjects were enrolled (screened and signed informed consent), 2741 subjects had completed Year 1 and 1008 subjects had completed Year 2. The SAE cut-off date of 30 April 2010 is the same as for REDUCE. For cases of prostate cancer, data are included through 8 June 2010. This study is ongoing and data are still being collected.

8.2. Visits and Assessments

Part A, 2-year observational study: Study visits include one clinic visit (a screening visit) and two telephone calls (approximately one year apart). The screening visit occurs as soon as possible after the REDUCE Year-4 Contact. Thereafter, subject and/or investigator reported information is recorded during annual phone calls (phone visit) in which the Investigator or designee interviews the subject. Visit schedules are modified depending on how soon the screening visit occurs after the REDUCE Year 4 Contact visit.

Data collected include patient-reported prostate cancer events, chronic concomitant medications, PSA results, prostate cancer treatment and SAEs. Subjects who have a for-cause prostate biopsy or surgery during this 2-year observation period will have representative slides or prostate tissue blocks collected from the local pathology laboratory and shipped to the central pathology laboratory for confirmatory review.

Part B, Prostate Biopsy Tissue Study: This part of the study was to allow potential collection of tissue blocks or unstained slides from positive biopsies in subjects diagnosed with prostate cancer during REDUCE for future biomarker research. As of 17 February 2010, it was decided that no prostate tissue research would be conducted. Because of the small number of subjects who were eligible and/or consented to Part B of the study it was felt that no meaningful scientific information would be gleaned and therefore it was decided to cancel Part B."

Data are collected when subjects have completed the Year 2 contact/visit. GSK is notified of prostate cancer cases as they occur during the study period.

8.3. Subject Enrollment

Of the 2795 subjects enrolled in Study ARI103094 as of 4 February 2010 a total of 2775 subjects had data available in-house. Each of the subjects was further divided by their treatment group in REDUCE and visits completed in study ARI103094. Enrollment status is summarized in Table 66. Almost equal numbers of subjects from the placebo and dutasteride monotherapy groups of REDUCE entered and completed Year 1 and Year 2 contacts in ARI103094.

Table 66 Summary of Enrollment and Completion of Study by REDUCE Treatment Groups for ARI103094

Treatment Group in REDUCE Status in ARI103094	Placebo N	Dutasteride N	Total N
Screened	1379	1396	2775
Completion Status	n (%)	n (%)	n (%)
Completed Year 1 contact	1221 (89)	1230 (88)	2451 (88)
Completed Year 2 contact	385 (28)	396 (28)	781 (28)
Contact Year 2 only[a]	116 (30)	120 (30)	236 (30)
Contact Year 1 and 2[a]	269 (70)	276 (70)	545 (70)

Screened=enrolled subjects with data in-house.

a. Denominator=number of subjects who completed Year 2

8.4. Biopsy Data and Use of 5ARIs

Table 67 summarizes the number of subjects participating in ARI103094 who have completed the Year 2 follow-up visit and have available data on biopsies and 5ARI use as of 30 April 2010. Subjects who were diagnosed with prostate cancer during REDUCE are excluded. At present the data are still being collected and are too limited to evaluate.

Table 67 Summary of Biopsy Data and 5ARI Use in Subjects Completing the 2-Year Visit as of 30 April 2010 by REDUCE Treatment Group for ARI103094

Treatment Group in REDUCE	Placebo N=310	Dutasteride N=338
All Biopsies	40	29
Needle Biopsy	31	19
Reasons for Needle Biopsy		
Rising PSA	26	19
Nodule on DRE	0	1
Missing	3	0
Surgery	12	12
Prostate Cancer		
Central Path	0	2
Local Path	3	6
Concurrent 5ARI		
Finasteride	22	19
Dutasteride	70	70

As of 08 June 2010, there were 14 cases of prostate cancer diagnosed by local pathology, reported since study start (Table 68). One of the 14 cases of prostate cancer was also reported as an SAE (Subject #5995). Of the 14 cases of prostate cancer, 9 occurred in subjects treated with dutasteride in REDUCE. Only one of these subjects continued on dutasteride during ARI103094. For subjects who developed prostate cancer, the number of days since the last dutasteride treatment in REDUCE to the diagnosis of prostate cancer in study ARI103094 ranged from 146 to 695; for placebo-treated patients, the number of days since the last treatment to the diagnosis of prostate cancer ranged from 109 to 1786 days. Gleason scores of the prostate cancers were: previous dutasteride:

Gleason score 6 – 5 subjects, Gleason score 7 (3 + 4) – 2 subjects, Gleason score 7 (4+3) – 2 subjects; previous placebo: Gleason score 6 – 4 subjects, Gleason score 9 – 1 subject. All of the cancers were detected by unscheduled for-cause biopsies, read by local laboratories and subject to a confirmatory review by Bostwick Laboratories using the classic Gleason scoring method.

Table 68 Cumulative Summary of Prostate Cancers in ARI103094 Through 08-Jun-2010

Subject Number		REDUCE Treatment	Gleason Score (Local Pathology)	Days Since Last REDUCE Treatment	Completed Year 2 in ARI103094
Observation Study (ARI103094)[a]	REDUCE Study (REDUCE)				
2029	100723	Placebo	6	109	No
4651	95491	Placebo	6	428	Yes
4735	95089	Placebo	6	225	No
5543	114108	Placebo	6	455	No
1667	102948	Placebo	9	1,786	No[b]
1181	102435	Dutasteride	6	302	Yes
2890	94476	Dutasteride	6	146	Yes
4502	121597	Dutasteride	6	187	No
4622	121258	Dutasteride	6	210	No
10150	96284	Dutasteride	6	668	Yes
5995	119392	Dutasteride	7(3+4)	346	No
6230	98370	Dutasteride	7(3+4)	217	Yes
2962	94352	Dutasteride	7(4+3)	695	Yes
4664	114129	Dutasteride	7(4+3)	518	Yes

a. Subjects in ARI103094 were not using dutasteride post REDUCE with the exceptions of 4622 (dutasteride) and 4735 (no therapy information provided).

b. Completion of year 2 data for subject #1667 was pending at the time of this report.

8.5. SAEs

Four deaths were reported in study ARI103094. Two deaths were reported in the sNDA (pulmonary embolism and malignant lung neoplasm), and two deaths occurred during the period of the 120-day Safety Update (cardiac arrest and chronic obstructive pulmonary disease). Three deaths were considered by the investigators as unrelated to REDUCE study medication, and investigator causality was unknown in one death.

Among SAEs reported as of 30 April 2010, the most common were cardiac disorders and renal and urinary disorders (Table 69). Table 69 includes SAEs for 4 subjects which were also reported in the sNDA as occurring in REDUCE after the clinical cut-off date of 11-May-2009: hypothermia, invertebral disk disorder; epididymitis and urethral stenosis, and hypertensive crisis. These SAEs are reported in both studies (REDUCE and ARI103094) due to overlapping reporting periods.

Table 69 Number of Subjects with SAEs by MedDRA System Organ Class During ARI103094 as of 30 April 2010

MedDRA System Organ Class	Previous REDUCE Treatment		Total
	Placebo	Dutasteride	
Cardiac disorders	13	12	25
Infections and infestations	6	12	18
Renal and urinary disorders	14	11	25
Gastrointestinal disorders	8	10	18
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11	9	20
Reproductive system and breast disorders	12	9	21
Nervous system disorders	10	7	17
General disorders and administration site conditions	1	5	6
Hepatobiliary disorders	1	5	6
Musculoskeletal and connective tissue disorders	7	5	12
Respiratory, thoracic and mediastinal disorders	2	4	6
Vascular disorders	3	4	7
Eye disorders	0	3	3
Injury, poisoning and procedural complications	2	3	5
Skin and subcutaneous tissue disorders	0	1	1
Surgical and medical procedures	2	1	3
Investigations	3	0	3
Psychiatric disorders	1	0	1
Social circumstances	1	0	1
Blood and lymphatic system disorders	1	0	1
Ear and labyrinth disorders	1	0	1

No study medication is provided for Study ARI103094. Subjects are free to take any medication, including dutasteride or another 5ARI.
A subject may have had more than one SAE and be counted in more than one SOC.

9. RISK MANAGEMENT

- The Risk Management Plan for dutasteride to reduce the risk of prostate cancer in men at increased risk of developing the disease is based on data from REDUCE and CombAT, considered in context with data from the pivotal studies in men with BPH and post-marketing experience.
- Current product labeling adequately addresses the known risks of sexual AEs, breast disorders, and allergic reactions, as well as the potential risks of male breast cancer and fetal harm. Data from CombAT and REDUCE related to these safety issues are consistent with current labeling. These safety issues are monitored by GSK using routine pharmacovigilance practices, in addition to labeling, and no additional risk management/minimization activities are proposed for these safety issues.
- The following additional risk management measures are proposed due to observed numerical differences in cardiac failure events (in REDUCE and CombAT) and high-grade prostate cancers (in REDUCE).
- *Cardiac failure*
- Current product labeling addresses the observed differences among treatment groups in the incidence of *cardiac failure* in the REDUCE and CombAT trials. These

differences are described in the Adverse Reactions section of the product labeling. In addition, GSK is evaluating the feasibility of using of epidemiological databases to further investigate any association between dutasteride use and risk of cardiac failure. Reports of serious cardiac failure events in ongoing clinical trials are identified on an ongoing basis and investigators are contacted for additional information where appropriate.

- *High-grade prostate cancer*
- The use of dutasteride for prostate cancer risk reduction is intended for men at increased risk of developing the disease, defined as those who have a prior negative biopsy due to clinical concern and have an elevated serum Prostate-Specific Antigen (PSA).
- The following risk management measures are proposed due to the finding of a higher incidence of high-grade prostate cancers with dutasteride compared to placebo in the REDUCE trial:
    - Current product labeling includes the below statements under "Warnings and Precautions" regarding the effects of dutasteride on PSA and on the use of PSA in prostate cancer detection.
        - men receiving dutasteride should have a new PSA baseline established after 6 months of treatment with dutasteride (in current labeling)
        - any confirmed increases in PSA levels from nadir while on dutasteride may signal the presence of prostate cancer and should be carefully evaluated even if those values are still within the normal range for men not taking a 5α-reductase inhibitor
    - Additional label revisions to the current "Warnings and Precautions" regarding the effects of dutasteride on PSA and the use of PSA in prostate cancer detection shown below, are proposed to advise prescribers regarding:
        - PSA should be monitored regularly thereafter
        - any confirmed increases from lowest PSA while on dutasteride may signal the presence of prostate cancer *(particularly high-grade cancer) or medication non-compliance* and should be carefully evaluated, even if PSA values are still within the normal range for men not taking a 5-alpha reductase inhibitor
        - in a 4-year study of patients at increased risk of developing prostate cancer, following establishment of a new PSA baseline (after 6 months of treatment), increases in PSA were more indicative of a prostate cancer diagnosis (particularly high grade cancer) in men receiving dutasteride compared with men receiving placebo
    - Proposed labeling also includes data from the REDUCE trial on Gleason score 8-10 prostate cancers overall and during Years 1-2 and Years 3-4 under "Clinical Studies."

- The results of REDUCE with regard to high-grade prostate cancer and the use and interpretation of PSA in men taking dutasteride will be highlighted in publications and educational materials directed toward prescribers.
- Spontaneous reports of prostate cancer will continue to be followed up with a targeted questionnaire to request additional information, including results of diagnostic tests, biopsy results, and histopathology results (including grade, Gleason score and stage), medical history, family history, risk factors for prostate cancer, prostate cancer treatment, and details about the temporal relationship between dutasteride use and cancer diagnosis.

10. BENEFIT: RISK AND CONCLUSIONS

10.1. Therapeutic Justification

Prostate cancer represents a particularly important and suitable target for risk reduction because of its high prevalence, associated morbidity and mortality, long latency period, and the challenges in differentiating between high grade (potentially lethal) cancers and low grade cancers. Although the majority of men diagnosed with prostate cancer have low grade disease, it is the most common non-cutaneous cancer in the US and the second leading cause of male cancer death in the developed world [American Cancer Society, 2010] and there is considerable morbidity associated with both diagnosis and current treatment options. Therefore, current management practices could benefit from approaches that address some of the existing challenges in clinical practice:

- the diagnosis of biologically low aggressive prostate cancers that are unlikely to spread beyond the prostate and,
- the over-treatment of biologically low aggressive prostate cancers, particularly because of the potentially long survival of patients and the long-lasting negative effects of some treatments

- Currently, there are no approved medications for prostate cancer risk reduction. However, recent AUA/ASCO guidelines based largely on the PCPT results, have recommended that asymptomatic men with a PSA ≤3.0 ng/mL who are regularly screened with PSA or are planning to undergo annual PSA screening for early detection of prostate cancer may benefit from a discussion on the benefits and risks of 5ARIs for prostate cancer risk reduction [Kramer, 2009]. They also recognized that even if risk reduction of prostate cancer does not translate to a reduction of mortality, the impact on reducing the diagnosis and associated morbidities is a relevant endpoint.

Dutasteride offers a favourable benefit risk profile for this indication for several reasons:

Dutasteride is superior to placebo in prostate cancer risk reduction (23% relative risk reduction) in a population of men at increased risk of the disease (over 4 years). Although there are many determinants of prostate cancer risk, in clinical practice an elevated PSA is the most common reason for biopsy. Therefore, when defining the population at increased risk of the disease, a reasonable approach is to include men with

an elevated serum PSA and a previous negative biopsy done for clinical concern. Such men often are rebiopsied because of further increases in PSA and have a high risk of a prostate cancer diagnosis, as demonstrated by the REDUCE trial and in the literature [Welch, 2007].

The effect of dutasteride on prostate cancer risk reduction was evident despite the known effect of decreasing prostate volume, which made prostate cancer diagnosis easier in the dutasteride group versus the placebo group. There was a highly significant reduction in low grade cancers (Gleason score ≤6) with no statistically significant difference in high grade tumors (Gleason score 7-10) over the 4-year study period. Although a difference in Gleason score 8-10 cancers was observed between the treatment groups, the incidence of these cancers remained the same in the dutasteride group over 4 years (0.5% in each time period), compared with a decline in the incidence in the placebo group from Years 1-2 (0.5%) to Years 3- 4 (<0.1%).

Because the effect of dutasteride to reduce the risk of prostate cancer decreased as Gleason score increased, it is important to note that dutasteride does not interfere with the ability of PSA to detect high grade tumors that may not be controlled by dutasteride.

Applying the recommendations for PSA monitoring in the dutasteride label and current PSA monitoring standards from NCCN for placebo-treated or untreated men, there were similar undetected high grade cancers in the dutasteride group compared to the placebo group (24% vs. 26%, respectively).

Of the Gleason score 8–10 cancers in the dutasteride subjects in REDUCE, 10 of 16 cancers during the first 2 years, and all of the 12 cancers during the second 2 years demonstrated a rising PSA from nadir. An additional 4 of the 16 cancers detected during the first 2 years also had rises from nadir, but since these occurred on the date of the biopsy they were not included in the count. If these subjects were included then 14 of the 16 subjects with Gleason 8-10 cancers demonstrated a rising PSA from nadir. If only dutasteride subjects who had a rising PSA during the study were biopsied, some cancers would have been undetected. The cancers that would have been undetected due to a lack of PSA rise had a lower mean volume on biopsy, demonstrating the difficulty of detecting small cancers using PSA, even if high-grade. From a clinical standpoint, these cancers as well as those that were detected by a rise in PSA from nadir appeared to be amenable to standard treatments.

By reducing the risk of biopsy detectable prostate cancer dutasteride treatment will result in a decrease in the number of subsequent aggressive interventions and medical treatments for prostate cancer management, a reduction in the number of days of hospitalizations and thus an expected overall decrease of the treatment associated morbidities that impact on patient's quality of life.

In addition by reducing PSA rises associated with BPH dutasteride treatment will reduce the number of for-cause biopsies and their associated morbidities. As shown in REDUCE if a patient undergoes a prostate biopsy the associated biopsy related complications will also be reduced by dutasteride treatment. Dutasteride treatment also showed significant reductions in prostate cancer precursor (HGPIN), and in prostate

cancer associated lesions (ASAP). This will result in less number of aggressive monitoring procedures being done to follow up these patients (including biopsies) with the resulting decrease in the associated morbidities.

Dutasteride offered significant additional benefits of improving BPH symptoms and reducing the risk of BPH-related outcomes. Dutasteride substantially improved BPH outcomes compared with placebo in men at increased risk of developing prostate cancer (77% risk reduction in AUR, 73% risk reduction in BPH-related surgery, 41% risk reduction in UTI). Quality of life was improved as measured by BPH QOL questionnaires.

Results from CombAT confirm the initial observations made in Phase III BPH trials of dutasteride and further support the value of dutasteride to reduce the risk of prostate cancer. The CombAT results help to extrapolate the findings of REDUCE to a population closer to the clinical setting where men are screened annually for prostate cancers with PSA and digital rectal exams and only for- cause biopsies are performed. In CombAT, there was an overall reduction of 34% and 41% in the prostate cancer diagnosis in the dutasteride monotherapy group and combination group, respectively, compared to the tamsulosin monotherapy group. This reduction was due to a reduced frequency of biopsy. In men undergoing prostate biopsy, the cancer detection rate was higher in men taking dutasteride compared to men taking tamsulosin. The reduction in prostate cancers with dutasteride was consistent among Gleason $\leq$6, 7, and 8-10 cancers. These results support the contention that dutasteride does not stimulate the growth of high grade cancers.

An important question for physicians will be for whom to prescribe dutasteride for prostate cancer risk reduction. Given the findings of this study, men with an elevated PSA and a negative biopsy done for a clinical concern (the REDUCE population) are the population that may clearly benefit from dutasteride's ability to reduce future cancer risk.

Once dutasteride treatment is initiated, a new baseline PSA should be established after approximately 6 months on therapy and monitored periodically. Any confirmed increases in PSA levels from nadir while on dutasteride may signal the presence of prostate cancer particularly high-grade cancer or medication noncompliance, and should be carefully evaluated. Any confirmed rise in PSA from start of dutasteride treatment may also signal the presence of prostate cancer.

10.2. Safety

The safety profile of dutasteride in BPH is well established, and the AE profile of dutasteride in REDUCE was generally consistent with its known safety profile in men with BPH, with two exceptions: cardiac failures and Gleason 8-10 cancers. Few subjects discontinued study drug prematurely or withdrew from the study. The low rate of discontinuations/withdrawals in the dutasteride group reflects a favorable tolerability profile and likely a positive patient perception of benefit/risk. The risk profile of dutasteride focuses on three aspects:

- An imbalance in reported events of cardiac failure was observed. Based on the totality of data from the dutasteride clinical trials program (>10,000 subjects exposed to dutasteride), including the meta-analyses from the clinical trials and the post-marketing data, no causal relationship between dutasteride, alone or in combination with an alpha blocker, has been established. The results of REDUCE and CombAT with respect to cardiac failure have been added to the product labeling under "Adverse Reactions".

- There were similar numbers of subjects with high grade tumors, defined as Gleason score 7-10, over the 4 year study period in dutasteride versus placebo treated subjects. There were fewer high grade Gleason 8-10 tumors in the placebo group compared with the dutasteride group in Years 3-4. Overall, in this previously biopsied population, the number of subjects diagnosed with Gleason score 8-10 cancers was low. The current AVODART label contains a "Warning and Precaution" (and description of the data from REDUCE) regarding the significance of increases in PSA relative to high-grade tumors.

- The occurrence of AEs related to sexual function and breast disorders was higher in the dutasteride group than the placebo group, consistent with data from previous studies and current product labeling. These AEs were generally mild or moderate, rarely lead to drug discontinuation, and in some subjects resolved while on therapy. Also, the rates of these AEs are lower than reported following prostate cancer interventions. When these events occur following surgical or radiation treatments for prostate cancer, they are often not reversible.

10.3. Risk Benefit Profile

Results in men who were at risk of prostate cancer indicate that dutasteride clinically and statistically significantly reduces the relative risk of biopsy-detectable prostate cancer compared to placebo (23%, $p<0.0001$). More subjects in the placebo group than in the dutasteride group were diagnosed with prostate cancer during the study (858/4073 subjects in the placebo group [21.1%] and 659/4049 subjects in the dutasteride group [16.3%]).This reduction in risk was consistent irrespective of age, family history of prostate cancer and baseline PSA level.

Additional benefits include:

- Fewer invasive surgical procedures or treatments for low-grade cancer, which would be expected to also decrease the complications from these interventions.
- Decreased incidence of HGPIN and ASAP, precursor and predictor lesions to prostate cancer respectively
- BPH-related benefits, including reduction in the following: BPH symptomatology, the need for alpha blockers, the risk of AUR, the need for BPH-related surgery, UTIs, and biopsy complications.
- Improved patient-reported outcomes in BPH endpoints (IPSS, Q8 of IPSS, and BII).
- QOL benefits related to decreased incidence of prostate cancer. Despite the majority of low-grade tumors being organ confined and slow growing, it has been found that

the diagnosis of prostate cancer has a significant, negative effect on vitality, social functioning, role-emotional, and mental status, as measured by the Short-Form 36-item Health Survey (SF-36). Further, a greater rate of anxiety has been seen in men diagnosed with early-stage (5.2%) and advanced-stage (5.8%) prostate cancer compared with prostate cancer-free age-matched controls in the general population [Love, 2008].

- QOL benefits related to decreased incidence of low grade tumors that may be treated with active surveillance/watchful waiting and associated cancer"worry"with documented decreases in the physical domain scores and sexual function scores of men with prostate cancer more than would have been expected from the aging process alone [Arrendondo, 2004].

The safety profile of dutasteride in the proposed patient population is generally consistent with the well characterized profile in the registered indications. Additional possible risks associated with the use of dutasteride in men at increased risk of prostate cancer are cardiac failure and the observation of a difference in the incidence of high grade tumors between dutasteride and placebo subjects in Years 3-4 of the REDUCE study. If PSA is monitored in accordance with the dutasteride label, i.e., confirmed increase from nadir, dutasteride did not adversely impact, and may have improved, the ability of PSA to detect high grade tumors. Hence, by carefully monitoring PSA in men taking dutasteride, high grade cancers should be detected with a rising PSA, even if PSA is within the normal range for men not taking dutasteride.

Based on current data, these possible risks can be managed, within the product labeling. Adverse reactions observed in REDUCE were generally events related to sexual function and breast disorders, which are known effects of 5ARIs and typically decline after the first year of use.

Based on limited information from the REDUCE trial, if a cancer is diagnosed while on dutasteride therapy, future responses of these prostate cancers to subsequent androgen deprivation therapy are favorable and similar to those observed in cancers detected in the placebo group. Nine Gleason score 7-10 cancers diagnosed in each treatment group in REDUCE subsequently received androgen deprivation therapy for Prostate cancer, There was a PSA decline in all subjects in both groups and 2 subjects in dutasteride and 3 subjects in the placebo group achieved the threshold of undetectable PSA (<0.10 ng/ml). Although limited by the sample size and the follow-up period (1-24 months), these data support previous literature observations suggesting that 5ARI treatments do not jeopardize responses of prostate cancers to subsequent hormonal treatments [Andriole, 1995; Brufsky, 1997, Orstein, 1998].

Currently, there is no approved drug therapy to reduce the risk of prostate cancer in men considered at risk. The successful completion of the pivotal REDUCE study demonstrates that dutasteride 0.5 mg once daily has the potential to improve current prostate cancer management practices and address the existing unmet medical needs. Given the totality of the data, the benefit risk profile of dutasteride for reducing the risk of prostate cancer in men who are at increased risk of developing the disease is favorable and supports the use of dutasteride for risk reduction of prostate cancer in men at increased risk of developing the disease.

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12. APPENDICES

12.1. Appendix A: Dutasteride Prostate Cancer Risk Reduction Clinical Program

Protocol	Protocol Title	Patient Population	Exposure	Status
Prostate Cancer Risk Reduction				
ARI40006 REDUCE	A randomised, double-blind, placebo-controlled, parallel group study of the efficacy and safety of dutasteride 0.5 mg administered orally once daily for 4 years to reduce the risk of biopsy-detectable prostate cancer.	8231 male subjects at increased risk of prostate cancer (age ≥50 and ≤75 years; France ≥50 and ≤71 years; negative prostate biopsy within 6 months; PSA ≥2.5 ng/mL and ≤10 ng/mL for men aged 50-60 years, and ≥ 3.0 ng/mL and ≤ 10 ng/mL for men aged >60 years	Dutasteride 0.5 mg or matched placebo Once daily for 4 years	4-year treatment and 4 month safety follow-up periods completed (SAE cut-off date 01-Dec-09)
ARI103094 (REDUCE Follow-Up)	Two year observational follow-up study for 4-year REDUCE study subjects	As of February 4th, 2010 there are 2795 subjects at increased risk of prostate cancer and who received investigational product (dutasteride or placebo) in REDUCE.	No investigational product	Ongoing
Supportive Studies				
ARI40005 CombAT	A randomised, double-blind, parallel group study to investigate the efficacy and safety of treatment with dutasteride (0.5 mg) and tamsulosin (0.4 mg), administered once daily for 4 years, alone and in combination, on the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic benign prostatic hyperplasia	4844 male subjects aged ≥ 50 years with a clinical diagnosis of BPH, and PSA ≥ 1.5ng/mL	Dutasteride 0.5 mg + placebo or tamsulosin 0.4 mg + placebo or dutasteride 0.5 mg + tamsulosin 0.4 mg Once daily for 4 years	4-year treatment and 4 month safety follow-up periods completed (SAE cut-off date 21 Aug 09)
AVO105948 REDEEM	A randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of dutasteride in extending the time to progression of low-risk, localized prostate cancer in men who are candidates for or undergoing expectant management	302 male subjects aged ≥ 50 years with a clinical diagnosis of clinical diagnosis localized prostate cancer (T1c-T2a), a Gleason score of ≤6 and/or a PSA ≤10ng/mL	Dutasteride 0.5 mg or placebo Once daily for 3 years	3 year treatment and 4 month safety follow-up Complete

12.2. Appendix B: Protocol Amendments for REDUCE

Amendment No.1	Genetic Research Protocol
Amendment No. 2	US only: Prohibition of blood donation for 6 months following last dose of dutasteride
Amendment No. 3	EU only: Recommended use of a condom whilst participating in the study
Amendment No. 4[a]	• Retrieval of prostatic surgery tissue for additional histopathologic evaluation • Collection of height and weight at end of study • Allowance for conduct of entry ECG anytime after informed consent and prior to randomization • Change in wording (from "must" to "should") with regard to 10-core entry biopsies • Correction of miscellaneous text errors
Amendment No. 5	Japan only: Addition of clinic visits at 1 and 3- months post-randomization; addition of routine hematology/chemistry assessments at Visit 3 (6 months post-randomization); prohibition of blood donation for 6 months following last dose of dutasteride
Amendment No. 6	Planned for Japan only- Administrative- Cancelled
Amendment No. 7	France only: Reduced age at entry from 75 to 71.
Amendment No. 8	Non-US- duplicate of US Amendment 2: Prohibition of blood donation for 6 months following last dose of dutasteride
Amendment No. 9[a]	Revisions to: inclusion criteria with respect to • total PSA and free PSA; • clarification of Ta bladder cancer • the allowance for the use of famotidine, metronidazole, and topical ketoconazole; the allowance for the use of cimetidine before entry into the study; • correction of a typo in Section 6.3.9 "Urinary Flow Measurement" which now includes peak flow equalling 5 mL/second. Incorporation of revisions from 5 previous amendments (Amendments 2, 3, 4, 7, and 8) into the main body of the protocol with the exception of Genetics Research (Amendment 1) and Japan Only (Amendment 5, which is summarized in Appendix 6 of Amendment 9).
Amendment No. 10	Bulgaria, Estonia, Hungary, Lithuania, Romania and Turkey: Exemption from completion of BII, MOS Sleep -6S and Problem Assessment scale of the SFI for
Amendment No.11[a]	Revisions to the inclusion/exclusion criteria by: • Removing the ≤25% free PSA requirement in inclusion criteria • Defining a 15% variability outside of the upper and lower limits of the total serum PSA range defined in inclusion criteria 1 to allow a single repeat assessment for study eligibility • Adding a one week allowance to the 6-month window prior to enrollment for a single, negative prostate biopsy (minimum 6 cores/maximum 12 cores) in inclusion criterion 1 • Allowing a single, repeat post void residual volume assessment if the volume is >200mL and <250mL for study eligibility • Adding "or procedure related "to the acceptable induced AUR causes in exclusion criterion 9 • Clarifying that basal and squamous cell carcinomas are not included in exclusion criterion 11 by re-arranging sentence order

	• Modifying exclusion criteria 16 to allow exposure to 5 alpha reductase inhibitors for less than 6 weeks not occurring during the 3 months prior to study entry • Addressing that the BII, MOS Sleep –6S and the PAS SFI may not be available as validated translations in some local languages in countries which may be involved in the study • Adding concurrent medications to the biannual follow-up via phone contact every 6 months (± 2 weeks) until the 4-year anniversary of randomization for subjects that prematurely discontinue • Modifying the specific visit requirements for urinary flow measurement, post void residual volume and prostate volume assessments to any time period before a subject is randomized • Adding "conduct physician assessment of eligibility" to the Visit 1 description in Section 14.2 to match the Time and Events table in Section 14.1
Amendment No. 12[a]	• Addition of an early end of study biopsy if the study discontinues prematurely • Modifying the follow-up of subjects diagnosed with prostate cancer during the study to 6-month clinic visits with assessments of total serum PSA, serum for continued biomarker storage, cancer staging, medications, selected events, and study-related SAE's through Visit 10 (Month 48) • Addition of language to Histopathologic Sub-Study for clarification of tissue collection and options in Section 6.3.7.1. • Addition of language regarding the need to determine PV by TRUS using the ellipsoidal formula to For-Cause Biopsies in Section 6.3.2.2. • Modifying the definition for Subject Completion in Section 9.1. • Allowing the study-mandated biopsy procedure at the 24 month and 48 month visits to be performed within 7 days after the scheduled visit date • Listing Testosterone as a specific example of an anabolic steroid, which is a prohibited medication by the protocol • Incorporating the genetics research protocol into the main protocol in Section 14.7. Appendix #7 • Addition of urine collection at the year 2 and 4 scheduled biopsy visits in the genetics research protocol
Amendment No.13	• Modifying the visit window for Visit 10 to allow greater scheduling flexibility. By extending the visit window, both subjects and sites will have more flexibility in scheduling upcoming Visit 10s/4-year biopsies, thereby ensuring, hopefully, that all subjects will attend Visit 10 and have a 4-Year biopsy by the planned end of the treatment period (30 DEC 2008). Visit 10 will be conducted 48 months (-1 month/ + 1 week) after randomization (Visit 2). This window for Visit 10 also applies to subjects in the Prostate Cancer Group (Visit 10P).

a. Major Protocol Amendments

12.3. Appendix C: PCa grading: classic and modified Gleason scoring

Prior to 1974, when Gleason scoring was developed, PCa was graded as well-, moderately-, poorly-, or un-differentiated. Over the last two decades, Gleason score has become the optimal and most common method of grading, as it takes into account the heterogeneity of PCa, and is a powerful prognostic factor [Harnden, 2007].

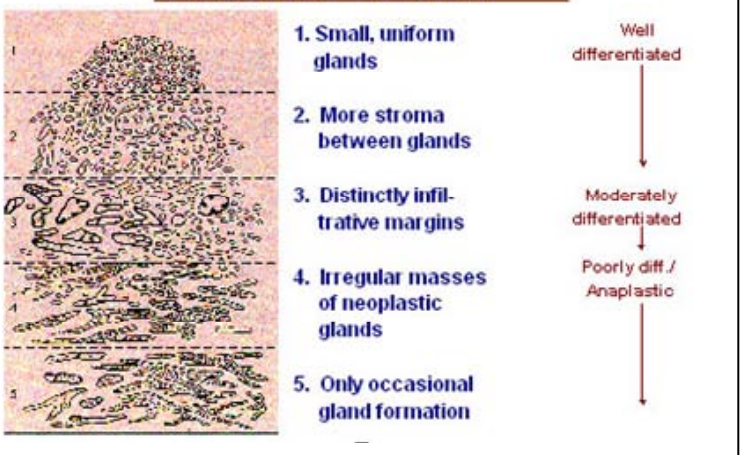

Figure 1. Gleason Pattern [SEER website, 2010]

The classic Gleason scoring system for prostatic carcinoma is based solely on the architectural pattern of the tumor. A grade of 1 to 5 (higher grade being less differentiated) is assigned to the predominant pattern and to the second most prevalent pattern in the specimen. In cases where the primary pattern is present in 95% of the specimen, the primary grade is used as both the primary and secondary grade, and the presence of a second grade in <5% of the specimen is noted but not considered in calculations of overall Gleason score. In all cases, where a third pattern exists, that pattern is noted by core, but not considered in the overall Gleason score calculation. The Gleason score is the sum of the primary and secondary grades and ranges from 2 to 10 [Gleason, 1992; Gleason, 1990]. Given that information comes from two different patterns, identical Gleason scores may confer different risks if the higher score is from the primary pattern. For example, with the same scores of 7, Gleason 4+3 is more aggressive than Gleason 3+4 [Harnden, 2007; Stark 2009; Pan, 2000].

Reflecting the evolving knowledge of PCa and the variations among pathologists in assigning Gleason score, the International Society of Urological Pathology (ISUP) published a series of consensus statements for the Gleason grading of prostate carcinoma, which included guidance for scoring both biopsy and prostatectomy specimens [Epstein, 2005]. The resulting "modified Gleason" consensus scoring statement simplified the calculation of overall Gleason scoring in biopsies by using the predominant pattern in the specimen as the primary score plus using the existence of any higher Gleason pattern, regardless of volume, as the secondary score. For example, using the

modified consensus scoring approach, a case with a primary Gleason pattern of 3 encompassing 98% of the cancer, and a secondary pattern of 4 encompassing 2% of the cancer would be scored overall as a 3+4= 7. Under the "classic" Gleason scoring approach, this same case would be graded overall as a 3+3 =6 because the secondary pattern was less than 5% of the total cancer. For biopsies, the consensus statement also recommended that a tertiary pattern replace the secondary pattern if the tertiary pattern is higher than both the primary and secondary patterns. In this regard, the consensus statement for prostatectomy specimens is different because the entire nodule is available for examination and Gleason score for prostatectomy is assigned by adding the primary and secondary patterns with a comment on tertiary pattern rather than adding the primary and highest score [Epstein, 2005]. Another area where the 2005 ISUP consensus statement on Gleason scoring differed from the classic Gleason scoring system was the classification of large cribriform glands as Gleason pattern 4 (previously classified as Gleason pattern 3). Smoothly circumscribed cribriform glands, which approximate the size of normal glands, continued to be classified as Gleason pattern 3.

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12.4. Appendix D: Gleason Score Tables

Table 70 Summary of Baseline Characteristics of Subjects by Gleason Scores in REDUCE

Baseline Characteristic		Placebo No PCa N= 2566	Dutasteride No PCa N= 2646	Placebo GS 5-6 N=617	Dutasteride GS 5-6 N=437	Placebo GS 7 N=214	Dutasteride GS 7 N=191	Placebo GS 8-10 N=19	Dutasteride GS 8-10 N=29
Age (Years)	Mean (SD)	62.3 (6.03)	62.5 (5.96)	63.2 (5.99)	63.5 (5.81)	65.0 (5.66)	64.5 (5.92)	66.4 (5.22)	64.8 (5.58)
Prostate Volume (cc)	Mean (SD)	46.2 (16.77)	46.6 (17.44)	44.0 (18.86)	44.3 (15.97)	41.0 (20.64)	39.0(15.21)	36.7 (10.94)	34.7(15.31)
Total PSA (ng/mL)	Mean (SD)	5.86 (1.95)	5.90 (1.91)	5.99 (1.87)	5.91 (1.87)	6.17 (1.83)	6.27 (1.91)	6.76 (1.94)	6.35 (2.28)
% Free PSA	Mean (SD)	16.99 (6.1)	16.91 (6.0)	16.07 (5.73)	16.56 (5.75)	15.13 (6.3)	13.83 (6.18)	13.71 (7.58)	12.74 (5.77)
PSA Density (ng/mL/cc)	Mean (SD)	0.14 (0.089)	0.14 (0.082)	0.16 (0.094)	0.15 (0.078)	0.19 (0.141)	0.19 (0.110)	0.20 (0.085)	0.22 (0.132)
Family PCa History:	Yes (n/%)	296 (12)	343 (13)	101 (16)	69 (16)	36 (17)	32 (17)	4 (21)	3 (10)
	No (n/%)	2270 (88)	2299 (87)	516 (84)	368 (84)	178 (83)	159 (83)	15 (79)	26 (90)

Note: For Gleason score analysis, only needle biopsies are considered.

Table 71 Individual Subjects with Gleason Score 8-10 Cancers in REDUCE

Subject Number	Age (yr)	Yr PCa DX	Base PSA	PSA NADIR	Final PSA before PCa Dx	% change from baseline to final PSA	% Change from Nadir to Final PSA	Base PV	PV at PCa Dx	% Change in PV from baseline to PCa	Overall Gleason sum	Number of cores positive for PCa	Avg % core involved over cancer slides	Sum cancer volume over cancer slides
Dutasteride														
92999	73	2	9.9	5.8	8	-19.2	37.9	63.2	62.4	-1.2	8	1	8	0.0008
93291	74	4	7.5	1.9	6.5	-13.3	242.1	68.4	51.8	-24.3	8	4	7.5	0.0033
95335	54	2	4.5	2.2	2.2	-51.1	0	48.4	31.2	-35.5	8	2	7.5	0.0016
95683	59	2	9.9	4	5.4	-45.5	35	49.4	67.5	36.7	9	6	10.7	0.0047
95884	62	4	7.2	6.3	12.7	76.4	101.6	46.5	NA	NA	9	5	37	0.008
95908	65	2	9.1	4.4	8.6	-5.5	95.5	29.9	20	-33.2	9	7	10.1	0.0084
95957	59	4	4.1	2.9	6.5	58.5	124.1	14.4	NA	NA	8	1	20	0.0024
97439	58	4	8.7	3.5	5.3	-39.1	51.4	17.8	21.8	22.5	9	2	37.5	0.0057
98775	58	4	4.6	2.9	6.2	34.8	113.8	22.8	31.5	38	9	7	21.1	0.0157
98878	68	4	5.1	2.1	6.7	31.4	219	19	33.5	76.1	9	5	70	0.0204
98921	66	4	4	1.3	1.8	-55.0	38.5	62.8	33.0	-47.5	8	2	50	0.0055
99004	62	2	8	8	8	0.0	0	37	NA	NA	8	1	5	NA
100049	65	4	7.6	3.5	25	227.6	611.4	55.3	NA	NA	10	3	43.3	0.0055
100444	67	2	9.8	3.4	4.2	-57.1	23.5	17.2	20	16.6	9	2	37.5	0.0047
100655	70	2	5	1.8	2.5	-50.0	38.9	28.3	NA	NA	8	2	30	0.0047
101206	63	2	3.5	1.4	1.4	-60.0	0	28.2	21.4	-24	9	1	10	0.0002
101261	66	4	3.1	1.6	2.4	-22.6	50	28.3	21.3	-24.8	9	3	40	0.0098
114139	73	4	8.8	3	8.2	-6.8	173.3	15	NA	NA	8	2	27.5	0.0041
118567	72	2	8.6	1.7	3.3	-61.6	94.1	55.3	36.8	-33.4	8	2	17.5	0.0031
120195	73	2	9.4	5.7	6.6	-29.8	15.8	34.6	25.3	-26.7	9	5	14.4	0.0102

Subject Number	Age (yr)	Yr PCa DX	Base PSA	PSA NADIR	Final PSA before PCa Dx	% change from baseline to final PSA	% Change from Nadir to Final PSA	Base PV	PV at PCa Dx	% Change in PV from baseline to PCa	Overall Gleason sum	Number of cores positive for PCa	Avg % core involved over cancer slides	Sum cancer volume over cancer slides
120729[a]	70	2	6.2	2.5	2.5	-59.7	0	32.7	26.9	-17.9	9	2	5.5	0.001
121310	57	2	4.4	1.1	1.1	-75.0	0	26	17.1	-34.4	9	1	10	0.0008
121375	64	2	4.9	1.6	1.6	-67.3	0	18.9	21.5	13.9	8	1	10	0.0008
121506	63	2	4.2	4.1	4.1	-2.4	0	29.2	32.2	10.6	9	2	21.5	0.004
122929	70	4	4.6	0.9	3.7	-19.6	311.1	36.7	19.5	-46.9	9	2	75	0.0102
124568	57	4	2.7	1	1.4	-48.1	40	36.9	26.3	-28.8	8	1	5	0.0008
140456	65	2	5.1	3.5	5.9	15.7	68.6	27.9	11.2	-59.9	9	3	8.3	0.002
142611[b]	65	2	7.1	5.9	7.5	5.6	27.1	27	27	0.1	9	3	38.3	0.0057
147614[c]	61	2	6.5	2.2	3.4	-47.7	54.5	29.4	29.9	1.5	8	3	36.7	0.0082

a: FH father, 73; b: brother, 58; c: father, 60 and grandfather.

Abbreviations: Base=baseline, Dx=diagnosis, FH= family history; PCa=prostate cancer, PSA=prostate specific antigen, PV=prostate volume, NA=not assessed

Subject Number	Age	YR PCa DX	Base PSA	PSA NADIR	Final PSA before PCa Dx	% change from baseline to final PSA	% Change from Nadir to Final PSA	Base PV	PV at PCa Dx	% Change in PV from baseline to PCa	Overall Gleason sum	Number of cores positive for PCa	Avg % core involved over cancer slides	Sum cancer volume over cancer slides
PLACEBO														
91921	65	2	9.9	9.9	17.5	76.8	76.8	43.7	47.2	8	9	3	27.5	0.0055
92501[a]	66	2	6.4	5.4	7.4	15.6	37	27.7	39.3	41.9	8	1	20	0.002
93194	68	2	7.6	7.6	7.6	0	0	21.5	NA	NA	8	3	30	0.0098
94333	63	2	6.9	6.9	8.5	23.2	23.2	40.4	39.5	-2.1	8	1	65	0.0039
94469	59	2	8.2	7.9	10.4	26.8	31.6	38.5	35.1	-8.7	8	2	9	0.001
95705	62	2	9.7	3.7	3.7	-61.9	0	27.6	27.1	-1.8	8	1	2	0.00003
95714	62	2	8.8	6	6	-31.8	0	41.6	22.2	-46.5	8	1	1	0.00003
97735[b]	57	2	5.9	5.9	12.9	118.6	118.6	23.8	NA	NA	8	1	10	0.0016
99902	71	2	7	3.2	3.2	-54.3	0	49.5	48.5	-2	9	3	30	0.0086
100711	64	2	6.6	5.4	6.1	-7.6	13	25.1	39.5	57.2	8	1	50	0.0031
116120	70	2	4.8	3.6	4.8	0	33.3	64.6	84.8	31.2	8	1	5	0.0002
117694	73	2	3.2	2.8	6.1	90.6	117.9	36.7	41.3	12.5	9	1	50	0.0031
118603	61	2	6.3	5.7	6.9	9.5	21.1	34.6	29.3	-15.3	8	1	3	0.0002
118964[c]	64	2	7.4	5.9	7.7	4.1	30.5	34.3	27.2	-20.6	9	1	10	0.0012
120925[d]	65	2	4.7	4.7	9.6	104.3	104.3	37.8	41.7	10.5	9	2	5	0.0016
122469	73	2	9.7	9.7	28.5	193.8	193.8	29.5	NA	NA	9	6	53.8	0.0297
125378	70	4	5.7	5.6	10.1	77.2	80.4	25.2	21.2	-16.1	9	1	60	0.0031
138122	74	2	5.9	5.1	8	35.6	56.9	49.3	50.7	2.8	9	3	24.7	0.0096
146112	74	2	3.7	3.7	6.9	86.5	86.5	45.18	NA	NA	8	1	50	0.0039

a: FH uncle, 70; b: father, 80; c: father, 62; d: father, 64.

Abbreviations: Base=baseline, Dx=diagnosis, FH= family history; PCa=prostate cancer, PSA=prostate specific antigen, PV=prostate volume, NA=not assessed,

Table 72 PSA changes and High Grade Tumors (Dutasteride: change from month 6 to final PSA, Placebo: PSA velocity of 0.35 ([PSA less than 4] and 0.75 ng/ml/yr [PSA greater than or equal to 4)] ng/ml/yr)

Treatment	PPV	NPV	Sensitivity	Specificity	Number of cancers undetected
Gleason grade 7-10					
Placebo	0.106	0.959	0.639	0.608	82
Dutasteride	0.132	0.960	0.571	0.734	93
Gleason grade 8-10					
Placebo	0.010	0.998	0.778	0.594	4
Dutasteride	0.020	0.996	0.679	0.717	9

NPV= negative predictive value; PPV= positive predictive value

Table 73 PSA changes & and High Grade Tumors (Dutasteride: change from nadir, Placebo: PSA velocity of 0.35 ([PSA less than 4] and 0.75 ng/ml/yr [PSA greater than or equal to 4)] ng/ml/yr)

Treatment	PPV	NPV	Sensitivity	Specificity	Number of cancers undetected
Gleason grade 7-10					
Placebo	0.106	0.959	0.639	0.608	82
Dutasteride	0.077	0.953	0.755	0.356	54
Gleason grade 8-10					
Placebo	0.010	0.998	0.778	0.594	4
Dutasteride	0.010	0.994	0.759	0.349	7

NPV= negative predictive value; PPV= positive predictive value

12.5. Appendix E: Safety Assessment Schedules in REDUCE and CombAT

		Treatment Period (Every Year for 4 Years)					
Month	S/B	3	6	9	12	EOT	FUp
Procedure	REDUCE / CombAT						
Adverse Events	X / X	X[a] / X	X[a] / X	X[a] / X	X[a] / X	X / X	X / X
Concomitant Meds	X / X	X[a] / X	X[a] / X	X[a] / X	X[a] / X	X / X	X / X
Vital Signs	X / X	NA / X	NA / X	NA / X	X / X	X / X	NA / X
PE[b] – DRE, Gynecomastia	X / X		NA / X		X / X	X[c] / X	NA / X[c]
Hematology/Clinical Chemistry	X[d] / X[d]				X / X	X / X	NA / X[e]
PSA	X[f] / X		X[f] / NA		X[f] / X	X[f] / X[f]	
PVR	X / X		NA / X		NA / X	NA / X	
Physician Assessment[g]	X / X		X / NA		X / NA		
ECG	X / X						

Note: grey shading indicates common assessments for REDUCE and ARI40005.
S=Screening; B=Baseline, EOT=End of Treatment; FUp=Follow-up telephone contact (REDUCE)/Follow-up visit (CombAT), NA=not assessed, PE=Physical Examination; PSA=prostate specific antigen; PVR=post-void residual volume

a. In REDUCE, AEs and concomitant medications were assessed in the clinic every 6 months starting at Month 6 and by telephone contact every 6 months starting at Month 3.
b. Height and weight measured at Baseline and at Month 48 or EOT in REDUCE and at Baseline for CombAT
c. Gynecomastia evaluation only
d. Fasting blood samples taken at Baseline for some subjects. Lipid panel, fasting insulin and glucose included
e. Performed only if clinically significant at previous visit
f. Assessment had to be at least 1 month after procedures performed on the prostate.
g. Physician determines if subject is eligible and safe to continue in the study.

Subjects diagnosed with PCa in REDUCE who participated in the PCa follow-up visited the clinic every 6 months from date of randomization to Month 48. Modified assessments and procedures at these visits included collection of total serum PSA and serum for biomarker storage, cancer staging at initial diagnosis and if subsequently updated, recording medications, review of medical history for specified clinical events and study drug/study-related SAEs.

12.6. Appendix F: Additional Safety Data Tables

Table 74 Number (%) of Subjects with Common Drug-Related AEs (>=1% in Any Group) by System Organ Class and Preferred Term (CombAT ITT Population)

System Organ Class Preferred Term	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)
Any drug-related AE	456 (28)	340 (21)	304 (19)
Reproductive system and breast disorders	295 (18)	194 (12)	153 (9)
Erectile dysfunction	142 (9)	114 (7)	84 (5)
Retrograde ejaculation	71 (4)	11 (<1)	19 (1)
Ejaculation failure	44 (3)	10 (<1)	15 (<1)
Gynaecomastia	29 (2)	37 (2)	15 (<1)
Breast tenderness	22 (1)	19 (1)	6 (<1)
Nipple pain	22 (1)	15 (<1)	5 (<1)
Psychiatric disorders	99 (6)	78 (5)	56 (3)
Libido decreased	63 (4)	48 (3)	31 (2)
Loss of libido	32 (2)	23 (1)	17 (1)
Investigations	47 (3)	21 (1)	30 (2)
Semen volume decreased	37 (2)	6 (<1)	15 (<1)
Nervous system disorders	42 (3)	38 (2)	45 (3)
Dizziness	28 (2)	15 (<1)	28 (2)
Gastrointestinal disorders	42 (3)	43 (3)	32 (2)
Renal and urinary disorders	20 (1)	12 (<1)	8 (<1)
Vascular disorders	20 (1)	12 (<1)	10 (<1)
Skin and subcutaneous tissue disorders	19 (1)	17 (1)	18 (1)
General disorders and administration site conditions	11 (<1)	19 (1)	13 (<1)

System Organ Class and Preferred Terms are in descending order according to the Combination group.
Combination= Dutasteride + Tamsulosin

Table 75 Subjects with Common (>= 3% in Any Group) AEs by SOC, Preferred Term and Year of Onset (REDUCE Safety Population)

System Organ Class Preferred Term	Placebo n (%)					Dutasteride n (%)				
	Month 0-6 N=4126	Month 7-12 N=3988	Year 2 N=3842	Year 3 N=3567	Year 4 N=3177	Month 0-6 N=4105	Month 7-12 N=3959	Year 2 N=3767	Year 3 N=3460	Year 4 N=3126
Any AE	1442 (35)	1164 (29)	1588 (41)	1376 (39)	1124 (35)	1626 (40)	1218 (31)	1559 (41)	1310 (38)	1066 (34)
Reproductive system and breast disorders	218 (5)	151 (4)	216 (6)	194 (5)	104 (3)	397 (10)	216 (5)	219 (6)	184 (5)	95 (3)
Erectile dysfunction	124 (3)	65 (2)	81 (2)	79 (2)	24 (<1)	252 (6)	94 (2)	88 (2)	68 (2)	20 (<1)
Infections and infestations	371 (9)	298 (7)	450 (12)	406 (11)	362 (11)	339 (8)	263 (7)	439 (12)	388 (11)	321 (10)
Nasopharyngitis	72 (2)	57 (1)	90 (2)	86 (2)	66 (2)	86 (2)	64 (2)	99 (3)	84 (2)	73 (2)
Gastrointestinal disorders	235 (6)	197 (5)	302 (8)	250 (7)	192 (6)	289 (7)	210 (5)	295 (8)	211 (6)	203 (6)
Musculoskeletal and connective tissue disorders	245 (6)	170 (4)	328 (9)	232 (7)	210 (7)	245 (6)	198 (5)	320 (8)	241 (7)	191 (6)
Psychiatric disorders	138 (3)	75 (2)	93 (2)	68 (2)	55 (2)	217 (5)	77 (2)	101 (3)	58 (2)	41 (1)
Libido decreased	48 (1)	16 (<1)	14 (<1)	8 (<1)	6 (<1)	105 (3)	29 (<1)	24 (<1)	10 (<1)	3 (<1)
Nervous system disorders	148 (4)	100 (3)	184 (5)	108 (3)	99 (3)	157 (4)	94 (2)	152 (4)	118 (3)	84 (3)
Skin and subcutaneous tissue disorders	82 (2)	58 (1)	95 (2)	77 (2)	47 (1)	109 (3)	71 (2)	92 (2)	69 (2)	67 (2)
Metabolism and nutritional disorders	91 (2)	69 (2)	108 (3)	75 (2)	92 (3)	104 (3)	59 (1)	98 (3)	91 (3)	80 (3)
Vascular disorders	103 (2)	89 (2)	126 (3)	96 (3)	94 (3)	102 (2)	80 (2)	128 (3)	131 (4)	98 (3)
Hypertension	78 (2)	63 (2)	79 (2)	61 (2)	60 (2)	64 (2)	62 (2)	90 (2)	91 (3)	67 (2)
Investigations	69 (2)	48 (1)	54 (1)	48 (1)	49 (2)	93 (2)	68 (2)	96 (3)	47 (1)	44 (1)
General disorders and administration site conditions	66 (2)	60 (2)	73 (2)	65 (2)	67 (2)	80 (2)	45 (1)	97 (3)	70 (2)	48 (2)
Respiratory, thoracic, and mediastinal disorders	97 (2)	63 (2)	133 (3)	118 (3)	78 (2)	78 (2)	66 (2)	96 (3)	81 (2)	63 (2)
Injury, poisoning and procedural complications	72 (2)	56 (1)	145 (4)	134 (4)	104 (3)	65 (2)	73 (2)	138 (4)	108 (3)	108 (3)
Cardiac disorders	85 (2)	51 (1)	110 (3)	76 (2)	79 (2)	62 (2)	56 (1)	81 (2)	76 (2)	73 (2)

Table 76 Number (%) of Subjects With Fatal SAEs by System Organ Class and Preferred Term (REDUCE Safety Population)

System Organ Class Preferred Term	Placebo N=4126 n (%)	Dutasteride N=4105 n (%)
Any fatal AE	74 (2)	70 (2)
Cardiac disorders	25 (<1)	25 (<1)
Myocardial infarction	13 (<1)	7 (<1)
Acute myocardial infarction	1 (<1)	4 (<1)
Cardiac failure acute	0	3 (<1)
Cardiac failure	1 (<1)	2 (<1)
Cardiac arrest	5 (<1)	1 (<1)
Cardio-respiratory arrest	1 (<1)	1 (<1)
Coronary artery disease	1 (<1)	1 (<1)
Arrhythmia	0	1 (<1)
Cardiac tamponade	0	1 (<1)
Cardiogenic shock	0	1 (<1)
Myocardial ischaemia	0	1 (<1)
Ventricle rupture	0	1 (<1)
Cardiopulmonary failure	0	1 (<1)
Postinfarction angina	0	1 (<1)
Arteriosclerosis coronary artery	1 (<1)	0
Cardiac disorder	1 (<1)	0
Coronary artery occlusion	1 (<1)	0
Coronary artery thrombosis	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23 (<1)	25 (<1)
Lung neoplasm malignant	5 (<1)	5 (<1)
Metastases to central nervous system	0	3 (<1)
Bladder cancer	0	2 (<1)
Metastatic malignant melanoma	0	2 (<1)
Metastases to liver	3 (<1)	1 (<1)
Colon cancer	2 (<1)	1 (<1)
Gastric cancer	2 (<1)	1 (<1)
Pancreatic carcinoma	2 (<1)	1 (<1)
Pancreatic carcinoma metastatic	1 (<1)	1 (<1)
Adenocarcinoma	0	1 (<1)
Brain neoplasm malignant	0	1 (<1)
Lung squamous cell carcinoma stage unspecified	0	1 (<1)
Metastases to pleura	0	1 (<1)
Non-Hodgkin's lymphoma	0	1 (<1)
Oesophageal carcinoma	0	1 (<1)
Rectal cancer	0	1 (<1)
Renal cancer metastatic	0	1 (<1)
Non-small cell lung cancer metastatic	0	1 (<1)
Benign neoplasm	0	1 (<1)
Metastatic neoplasm	0	1 (<1)
Oesophageal neoplasm	0	1 (<1)
Hepatic neoplasm malignant	2 (<1)	0
Bone neoplasm malignant	1 (<1)	0
Bronchial carcinoma	1 (<1)	0
Colon cancer metastatic	1 (<1)	0
Leukaemia	1 (<1)	0
Lung adenocarcinoma	1 (<1)	0
Lymphoma	1 (<1)	0
Lung cancer metastatic	1 (<1)	0
Lymphoproliferative disorder	1 (<1)	0

System Organ Class Preferred Term	Placebo N=4126 n (%)	Dutasteride N=4105 n (%)
Metastases to lung	1 (<1)	0
Infections and infestations	3 (<1)	7 (<1)
Pneumonia	1 (<1)	3 (<1)
Septic shock	1 (<1)	1 (<1)
Sepsis	0	1 (<1)
Urinary tract infection	0	1 (<1)
Candida sepsis	0	1 (<1)
Endocarditis	1 (<1)	0
Nervous system disorders	9 (<1)	5 (<1)
Cerebrovascular accident	5 (<1)	3 (<1)
Dementia	0	1 (<1)
Motor neurone disease	0	1 (<1)
Amyotrophic lateral sclerosis	1 (<1)	0
Cerebrovascular disorder	1 (<1)	0
Convulsion	1 (<1)	0
Syringomyelia	1 (<1)	0
Injury, poisoning and procedural complications	3 (<1)	4 (<1)
Road traffic accident	1 (<1)	2 (<1)
Injury	0	1 (<1)
Subdural haemorrhage	0	1 (<1)
Post procedural haemorrhage	0	1 (<1)
Crush injury	0	1 (<1)
Head injury	1 (<1)	0
Overdose	1 (<1)	0
General disorders and administration site conditions	2 (<1)	4 (<1)
Multi-organ failure	0	2 (<1)
Death	2 (<1)	1 (<1)
Sudden death	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	4 (<1)	3 (<1)
Pulmonary embolism	1 (<1)	1 (<1)
Acute pulmonary oedema	0	1 (<1)
Pulmonary congestion	0	1 (<1)
Sleep apnoea syndrome	0	1 (<1)
Chronic obstructive pulmonary disease	2 (<1)	0
Bronchitis chronic	1 (<1)	0
Vascular disorders	6 (<1)	2 (<1)
Aortic aneurysm	1 (<1)	1 (<1)
Aortic rupture	1 (<1)	1 (<1)
Aneurysm ruptured	2 (<1)	0
Aortic aneurysm rupture	1 (<1)	0
Haemorrhage	1 (<1)	0
Hypertension	1 (<1)	0
Gastrointestinal disorders	2 (<1)	1 (<1)
Peritonitis	0	1 (<1)
Gastric ulcer	1 (<1)	0
Hepatobiliary disorders	0	1 (<1)
Cholecystitis acute	0	1 (<1)
Immune system disorders	0	1 (<1)
Polyarteritis nodosa	0	1 (<1)
Investigations	0	1 (<1)
Blood pressure decreased	0	1 (<1)

Table 77 Laboratory Analytes and Threshold Value Multiplicative Factors

Laboratory Test	Multiplicative Factors	
	Lower	Upper
Hematology		
White Blood Cell Count (WBC)	0.5	3.0
Platelet Count	0.75	1.5
Hemoglobin	0.75	NS
Mean Cell Volume (MCV)	0.9	1.1
Serum Chemistry		
Glucose	0.7	1.75
Sodium	0.9	1.15
Potassium	0.75	1.4
Total Protein	0.8	1.15
Total Bilirubin	-	2.5
Albumin	0.9	1.2
Aspartate transaminase (AST) [SGOT]	-	3.0
Alanine transaminase (ALT) [SGPT]	-	3.0
Alkaline Phosphatase	-	1.5
Creatinine	0.5	3.0

NS=not specified

Table 78 Summary of Shifts in Hematological Parameters from Baseline to Final Assessment (REDUCE Safety Population)

Hematology Parameter	N	Transition from baseline				
		Decrease from Baseline[a]		No Change[c]	Increase from Baseline[a]	
		Decrease to Low [b]	Decrease to Normal		Increase to Normal	Increase to High[d]
Placebo						
White blood cell (WBC)	3868	96	42	3570	91	69
Platelet count	3844	28	13	3740	24	39
Haemoglobin	3869	153	31	3449	182	54
MCV	3869	26	49	3727	21	46
Dutasteride						
WBC	3848	95	36	3553	89	75
Platelets	3833	26	13	3737	30	27
Haemoglobin	3851	177	34	3420	175	45
MCV	3851	25	55	3712	13	46

a. Status at the final assessment.
b. Includes subjects who were either Normal or High at baseline and reported Low at the final assessment.
c. Includes subjects whose baseline status remained unchanged at the final assessment.
d. Includes subjects who were either Normal or Low at baseline and reported High at the final assessment.

Table 79 Summary of Shifts in Liver Function Parameters from Baseline to Final Assessment (REDUCE Safety Population)

Chemistry Parameter	N	Transition from baseline				
		Decrease from Baseline[a]		No Change[c]	Increase from Baseline[a]	
		Decrease to Low [b]	Decrease to Normal		Increase to Normal	Increase to High[d]
Placebo						
Total Bilirubin	3900	0	94	3716	0	90
AST	3899	0	40	3819	0	40
ALT	3900	0	97	3717	0	86
ALP	3900	0	23	3823	1	53
Dutasteride						
Total Bilirubin	3872	0	98	3686	0	88
AST	3872	0	27	3797	0	48
ALT	3872	0	79	3724	0	69
ALP	3872	0	33	3809	1	29

a. Status at the final assessment.
b. Includes subjects who were either Normal or High at baseline and reported Low at the final assessment.
c. Includes subjects whose baseline status remained unchanged at the final assessment.
d. Includes subjects who were either Normal or Low at baseline and reported High at the final assessment.

Table 80 Vital Signs Threshold Ranges

Vital Sign	Threshold Ranges	
	Lower	Upper
Systolic Blood Pressure (mmHg)	<80	>165
Diastolic Blood Pressure (mmHg)	<40	>105
Heart Rate (beats/minute)	<40	>100

mmHg=millimetres of mercury

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVODART safely and effectively. See full prescribing information for AVODART.

AVODART (dutasteride) Soft Gelatin Capsules
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Effects on Prostate-Specific Antigen (PSA) and the Use of PSA in Prostate Cancer Detection (5.3) 6/2010

----------INDICATIONS AND USAGE----------
AVODART, a 5α-reductase inhibitor, is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to: (1.1)

- improve symptoms,
- reduce the risk of acute urinary retention, and
- reduce the risk of the need for BPH-related surgery.

AVODART in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------
Monotherapy: 0.5 mg once daily. (2.1)
Combination with tamsulosin: 0.5 mg once daily and tamsulosin 0.4 mg once daily. (2.2)
Dosing considerations: Swallow whole. May take with or without food. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
0.5-mg soft gelatin capsules (3)

----------CONTRAINDICATIONS----------

- Pregnancy and women of childbearing potential. (4, 5.1, 8.1)
- Pediatric patients. (4)
- Patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to AVODART or other 5α-reductase inhibitors. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Women who are pregnant or may become pregnant should not handle AVODART Capsules. (5.1, 8.1)
- Patients should be assessed to rule out other urological diseases, including prostate cancer, prior to prescribing AVODART. (5.2)
- AVODART reduces total serum prostate-specific antigen (PSA) concentration by approximately 50%. Any confirmed increases in PSA levels from nadir while on AVODART should be evaluated for the presence of prostate cancer. (5.3)
- Patients should not donate blood until 6 months after their last dose. (5.4)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions, reported in ≥1% of patients treated with AVODART and more commonly than in patients treated with placebo, are impotence, decreased libido, ejaculation disorders, and breast disorders. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Use with caution in patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ritonavir). (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: June 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy

AVODART® (dutasteride) Soft Gelatin Capsules are indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

- improve symptoms,

- reduce the risk of acute urinary retention (AUR), and
- reduce the risk of the need for BPH-related surgery.

1.2 Combination With Alpha-Blocker

AVODART in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

2 DOSAGE AND ADMINISTRATION

The capsules should be swallowed whole and not chewed or opened, as contact with the capsule contents may result in irritation of the oropharyngeal mucosa. AVODART may be administered with or without food.

2.1 Monotherapy

The recommended dose of AVODART is 1 capsule (0.5 mg) taken once daily.

2.2 Combination With Alpha-Blocker

The recommended dose of AVODART is 1 capsule (0.5 mg) taken once daily and tamsulosin 0.4 mg taken once daily.

2.3 Dosage Adjustment in Specific Populations

No dose adjustment is necessary for patients with renal impairment or for the elderly *[see Clinical Pharmacology (12.3)]*. Due to the absence of data in patients with hepatic impairment, no dosage recommendation can be made *[see Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

0.5 mg, opaque, dull yellow, gelatin capsules imprinted with “GX CE2” in red ink on one side.

4 CONTRAINDICATIONS

AVODART is contraindicated for use in:

- Pregnancy. Dutasteride inhibits the activity of 5α-reductase, which prevents conversion of testosterone to dihydrotestosterone, a hormone necessary for normal development of male genitalia. In animal reproduction and developmental toxicity studies, dutasteride inhibited development of male fetus external genitalia. Therefore, AVODART may cause fetal harm when administered to a pregnant woman. If AVODART is used during pregnancy or if the patient becomes pregnant while taking AVODART, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*.
- Women of childbearing potential *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*.
- Pediatric patients *[see Use in Specific Populations (8.4)]*.
- Patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to AVODART or other 5α-reductase inhibitors.

5 WARNINGS AND PRECAUTIONS

5.1 Exposure of Women—Risk to Male Fetus

AVODART Capsules should not be handled by a woman who is pregnant or who may become pregnant. Dutasteride is absorbed through the skin and could result in unintended fetal exposure. If a woman who is pregnant or who may become pregnant comes in contact with leaking dutasteride capsules, the contact area should be washed immediately with soap and water *[see Use in Specific Populations (8.1)]*.

5.2 Evaluation for Other Urological Diseases

Lower urinary tract symptoms of BPH can be indicative of other urological diseases, including prostate cancer. Patients should be assessed to rule out prostate cancer and other urological diseases prior to treatment with AVODART and periodically thereafter. Patients with a large residual urinary volume and/or severely diminished urinary flow may not be good candidates for 5α-reductase inhibitor therapy and should be carefully monitored for obstructive uropathy.

5.3 Effects on Prostate-Specific Antigen (PSA) and the Use of PSA in Prostate Cancer Detection

Dutasteride reduces total serum PSA concentration by approximately 40% following 3 months of treatment and by approximately 50% following 6, 12, and 24 months of treatment. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Therefore, for interpretation of serial PSAs in a man taking AVODART, a new baseline PSA concentration should be established after 3 to 6 months of treatment, and this new value should be used to assess potentially cancer-related changes in PSA. To interpret an isolated PSA value in a man treated with AVODART for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated men. Any confirmed increases in PSA levels from nadir while on AVODART may signal the presence of prostate cancer and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-alpha reductase inhibitor.

The free-to-total PSA ratio (percent free PSA) remains constant at Month 12, even under the influence of AVODART. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men receiving AVODART, no adjustment to its value appears necessary.

Coadministration of tamsulosin with dutasteride resulted in similar changes to total PSA as dutasteride monotherapy.

5.4 Blood Donation

Men being treated with dutasteride should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

5.5 Effect on Semen Characteristics

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 (n = 27 dutasteride, n = 23 placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from

baseline in total sperm count, semen volume, and sperm motility were 23%, 26%, and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all semen parameters at all time-points remained within the normal ranges and did not meet predefined criteria for a clinically significant change (30%), 2 subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

Monotherapy:

- The most common adverse reactions reported in subjects receiving AVODART were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), and ejaculation disorders.
- Study withdrawal due to adverse reactions occurred in 4% of subjects receiving AVODART and 3% of subjects receiving placebo. The most common adverse reaction leading to study withdrawal was impotence (1%).

Over 4,300 male subjects with BPH were randomly assigned to receive placebo or 0.5-mg daily doses of AVODART in 3 identical 2-year, placebo-controlled, double-blind, Phase 3 treatment studies, each with 2-year open-label extensions. During the double-blind treatment period, 2,167 male subjects were exposed to AVODART, including 1,772 exposed for 1 year and 1,510 exposed for 2 years. When including the open-label extensions, 1,009 male subjects were exposed to AVODART for 3 years and 812 were exposed for 4 years. The population was aged 47 to 94 years (mean age, 66 years) and greater than 90% Caucasian. Table 1 summarizes clinical adverse reactions reported in at least 1% of subjects receiving AVODART and at a higher incidence than subjects receiving placebo.

Table 1. Adverse Reactions Reported in ≥1% of Subjects Over a 24-Month Period and More Frequently in the Group Receiving AVODART Than the Placebo Group (Randomized, Double-Blind, Placebo-Controlled Studies Pooled) by Time of Onset

Adverse Reactions AVODART (n) Placebo (n)	Adverse Reaction Time of Onset Month 0-6 (n = 2,167) (n = 2,158)	 Month 7-12 (n = 1,901) (n = 1,922)	 Month 13-18 (n = 1,725) (n = 1,714)	 Month 19-24 (n = 1,605) (n = 1,555)
Impotence				
AVODART	4.7%	1.4%	1.0%	0.8%
Placebo	1.7%	1.5%	0.5%	0.9%
Decreased libido				
AVODART	3.0%	0.7%	0.3%	0.3%
Placebo	1.4%	0.6%	0.2%	0.1%
Ejaculation disorders				
AVODART	1.4%	0.5%	0.5%	0.1%
Placebo	0.5%	0.3%	0.1%	0.0%
Breast disorders[a]				
AVODART	0.5%	0.8%	1.1%	0.6%
Placebo	0.2%	0.3%	0.3%	0.1%

[a] Includes breast tenderness and breast enlargement.

Long-Term Treatment (Up to 4 Years): There is no evidence of increased drug-related sexual adverse reactions (impotence, decreased libido, and ejaculation disorder) or breast disorders with increased duration of treatment. The relationship between long-term use of AVODART and male breast neoplasia is currently unknown.

Combination with Alpha-Blocker Therapy (CombAT):

- The most common adverse reactions reported in subjects receiving combination therapy (AVODART plus tamsulosin) were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), ejaculation disorders, and dizziness. Over 2 years of treatment, drug-related ejaculation disorders occurred more frequently in subjects receiving combination therapy (9%) compared to AVODART (2%) or tamsulosin (3%) as monotherapy.
- Study withdrawal due to adverse reactions occurred in 5% of subjects receiving combination therapy (AVODART plus tamsulosin) and 3% of subjects receiving AVODART or tamsulosin as monotherapy. The most common adverse reaction leading to study withdrawal in subjects receiving combination therapy was impotence (1%).

Over 4,800 male subjects with BPH were randomly assigned to receive either 0.5-mg AVODART, 0.4-mg tamsulosin, or combination therapy (0.5-mg AVODART plus 0.4-mg

tamsulosin) administered once daily in a 4-year double-blind study. Adverse reaction information over the first 2 years of treatment is presented below; information for years 2 to 4 is not yet available. During the first 2 years, 1,623 subjects received monotherapy with AVODART; 1,611 subjects received monotherapy with tamsulosin; and 1,610 subjects received combination therapy. The population was aged 49 to 88 years (mean age, 66 years) and 88% Caucasian. Table 2 summarizes adverse reactions reported in at least 1% of subjects in any treatment group.

Table 2. Adverse Reactions Reported Over a 24-Month Period in ≥1% of Subjects in Any Treatment Group (CombAT) by Time of Onset

	Adverse Reaction Time of Onset			
Adverse Reactions	Month 0-6	Month 7-12	Month 13-18	Month 19-24
Combination (n)[a]	(n = 1,610)	(n = 1,524)	(n = 1,424)	(n = 1,345)
AVODART (n)	(n = 1,623)	(n = 1,547)	(n = 1,457)	(n = 1,378)
Tamsulosin (n)	(n = 1,611)	(n = 1,542)	(n = 1,468)	(n = 1,363)
Impotence				
Combination	5.5%	1.2%	0.8%	0.3%
AVODART	3.9%	1.2%	0.6%	0.7%
Tamsulosin	2.7%	0.8%	0.4%	0.4%
Decreased libido				
Combination	4.5%	0.9%	0.4%	<0.1%
AVODART	3.3%	0.6%	0.7%	0.2%
Tamsulosin	1.9%	0.6%	0.4%	0.2%
Ejaculation disorders				
Combination	7.6%	1.6%	0.4%	<0.1%
AVODART	1.1%	0.6%	0.1%	0.1%
Tamsulosin	2.2%	0.5%	0.4%	0.1%
Breast disorders[b]				
Combination	1.0%	1.1%	0.7%	0.3%
AVODART	0.9%	1.0%	0.8%	0.5%
Tamsulosin	0.4%	0.4%	0.2%	0.1%
Dizziness				
Combination	1.1%	0.4%	0.2%	0.0%
AVODART	0.4%	0.2%	<0.1%	<0.1%
Tamsulosin	0.9%	0.5%	0.3%	0.1%

[a] Combination = AVODART 0.5 mg once daily plus tamsulosin 0.4 mg once daily.

[b] Includes breast tenderness and breast enlargement.

Cardiac Failure: In CombAT, after 4 years of treatment, the incidence of the composite term cardiac failure in the combination therapy group (12/1,610; 0.7%) was higher than in either monotherapy group: AVODART, 2/1,623 (0.1%) and tamsulosin, 9/1,611 (0.6%). Composite cardiac failure was also examined in a separate 4-year placebo-controlled trial evaluating AVODART in men at risk for development of prostate cancer. The incidence of cardiac failure in subjects taking AVODART was 0.6% (26/4,105) compared to 0.4% (15/4,126) in subjects on placebo. A majority of subjects with cardiac failure in both studies had co-morbidities associated with an increased risk of cardiac failure. Therefore, the clinical significance of the numerical imbalances in cardiac failure is unknown. No causal relationship between AVODART, alone or in combination with tamsulosin, and cardiac failure has been established. No imbalance was observed in the incidence of overall cardiovascular adverse events in either study.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of AVODART. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to AVODART.

Immune System Disorders: Hypersensitivity reactions, including rash, pruritus, urticaria, localized edema, serious skin reactions, and angioedema.

7 DRUG INTERACTIONS

7.1 Cytochrome P450 3A Inhibitors

Dutasteride is extensively metabolized in humans by the CYP3A4 and CYP3A5 isoenzymes. The effect of potent CYP3A4 inhibitors on dutasteride has not been studied. Because of the potential for drug-drug interactions, use caution when prescribing AVODART to patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ritonavir) *[see Clinical Pharmacology (12.3)]*.

7.2 Alpha-Adrenergic Blocking Agents

The administration of AVODART in combination with tamsulosin or terazosin has no effect on the steady-state pharmacokinetics of either alpha-adrenergic blocker. The effect of administration of tamsulosin or terazosin on dutasteride pharmacokinetic parameters has not been evaluated.

7.3 Calcium Channel Antagonists

Coadministration of verapamil or diltiazem decreases dutasteride clearance and leads to increased exposure to dutasteride. The change in dutasteride exposure is not considered to be clinically significant. No dose adjustment is recommended *[see Clinical Pharmacology (12.3)]*.

7.4 Cholestyramine

Administration of a single 5-mg dose of AVODART followed 1 hour later by 12 g of

cholestyramine does not affect the relative bioavailability of dutasteride *[see Clinical Pharmacology (12.3)]*.

7.5 Digoxin

AVODART does not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks *[see Clinical Pharmacology (12.3)]*.

7.6 Warfarin

Concomitant administration of AVODART 0.5 mg/day for 3 weeks with warfarin does not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of warfarin on prothrombin time *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X. *[See Contraindications (4)]*. AVODART is contraindicated for use in women of childbearing potential and during pregnancy. AVODART is a 5α-reductase inhibitor that prevents conversion of testosterone to dihydrotestosterone (DHT), a hormone necessary for normal development of male genitalia. In animal reproduction and developmental toxicity studies, dutasteride inhibited normal development of external genitalia in male fetuses. Therefore, AVODART may cause fetal harm when administered to a pregnant woman. If AVODART is used during pregnancy or if the patient becomes pregnant while taking AVODART, the patient should be apprised of the potential hazard to the fetus.

Abnormalities in the genitalia of male fetuses is an expected physiological consequence of inhibition of the conversion of testosterone to 5α-dihydrotestosterone (DHT) by 5α-reductase inhibitors. These results are similar to observations in male infants with genetic 5α-reductase deficiency. Dutasteride is absorbed through the skin. To avoid potential fetal exposure, women who are pregnant or may become pregnant should not handle AVODART Soft Gelatin Capsules. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water. Dutasteride is secreted into male semen. The highest measured semen concentration of dutasteride in treated men was 14 ng/mL. Assuming exposure of a 50-kg woman to 5 mL of semen and 100% absorption, the woman's dutasteride concentration would be about 0.175 ng/mL. This concentration is more than 100 times less than concentrations producing abnormalities of male genitalia in animal studies. Dutasteride is highly protein bound in human semen (>96%), which may reduce the amount of dutasteride available for vaginal absorption *[see Warnings and Precautions (5.1)]*.

In an embryo-fetal development study in female rats, oral administration of dutasteride at doses 10 times less than the maximum recommended human dose (MRHD) resulted in abnormalities of male genitalia in the fetus, and nipple development, hypospadias, and distended preputial glands in male offspring. An increase in stillborn pups was observed at 111 times the MRHD, and reduced fetal body weight was observed at doses ≥15 times the MRHD. Increased incidences of skeletal variations considered to be delays in ossification

associated with reduced body weight were observed at doses ≥56 times the MRHD. Abnormalities of male genitalia were also observed in an oral pre- and post-natal development study in rats and in 2 embryo-fetal studies in rabbits at one-third the MRHD.

In an embryo-fetal development study, pregnant rhesus monkeys were exposed intravenously to a dutasteride blood level comparable to the dutasteride concentration found in human semen. The development of male external genitalia of monkey offspring was not adversely affected. Reduction of fetal adrenal weights, reduction in fetal prostate weights, and increases in fetal ovarian and testis weights were observed in monkeys *[see Nonclinical Toxicology (13.3)]*.

8.3 Nursing Mothers

AVODART should not be used by nursing women. It is not known whether dutasteride is excreted in human milk.

8.4 Pediatric Use

AVODART is contraindicated for use in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of 2,167 male subjects treated with AVODART in 3 clinical studies, 60% were 65 and over and 15% were 75 and over. No overall differences in safety or efficacy were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dose adjustment is necessary for AVODART in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients. However, in a clinical study where 60 subjects received 5 mg (10 times the therapeutic dose) daily for 24 weeks, no additional adverse events were observed compared with those observed at the therapeutic dose of 0.5 mg *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

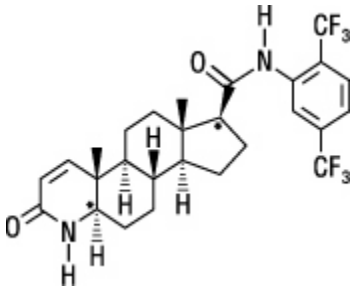
In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In a clinical study, daily doses of 5 mg (10 times the therapeutic dose) were administered to 60 subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

There is no specific antidote for dutasteride. Therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate, taking the long half-life of dutasteride into consideration.

11 DESCRIPTION

AVODART is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5α-reductase, an intracellular enzyme that converts testosterone to DHT.

Dutasteride is chemically designated as (5α,17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is $C_{27}H_{30}F_6N_2O_2$, representing a molecular weight of 528.5 with the following structural formula:



Dutasteride is a white to pale yellow powder with a melting point of 242° to 250°C. It is soluble in ethanol (44 mg/mL), methanol (64 mg/mL), and polyethylene glycol 400 (3 mg/mL), but it is insoluble in water.

Each AVODART Soft Gelatin Capsule, administered orally, contains 0.5 mg of dutasteride dissolved in a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. The inactive excipients in the capsule shell are gelatin (from certified BSE-free bovine sources), glycerin, and ferric oxide (yellow). The soft gelatin capsules are printed with edible red ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dutasteride inhibits the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme 5α-reductase, which exists as 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues, while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver.

Dutasteride is a competitive and specific inhibitor of both type 1 and type 2 5α-reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under in vitro and in vivo conditions and is extremely slow. Dutasteride does not bind to the human androgen receptor.

12.2 Pharmacodynamics

Effect on 5α-Dihydrotestosterone and Testosterone: The maximum effect of daily doses of dutasteride on the reduction of DHT is dose dependent and is observed within 1 to 2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT

concentrations were reduced by 85% and 90%, respectively. In patients with BPH treated with dutasteride 0.5 mg/day for 4 years, the median decrease in serum DHT was 94% at 1 year, 93% at 2 years, and 95% at both 3 and 4 years. The median increase in serum testosterone was 19% at both 1 and 2 years, 26% at 3 years, and 22% at 4 years, but the mean and median levels remained within the physiologic range.

In patients with BPH treated with 5 mg/day of dutasteride or placebo for up to 12 weeks prior to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were significantly lower in the dutasteride group compared with placebo (784 and 5,793 pg/g, respectively, $P<0.001$). Mean prostatic tissue concentrations of testosterone were significantly higher in the dutasteride group compared with placebo (2,073 and 93 pg/g, respectively, $P<0.001$).

Adult males with genetically inherited type 2 5α-reductase deficiency also have decreased DHT levels. These 5α-reductase deficient males have a small prostate gland throughout life and do not develop BPH. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to 5α-reductase deficiency have been observed in these individuals.

Effects on Other Hormones: In healthy volunteers, 52 weeks of treatment with dutasteride 0.5 mg/day (n = 26) resulted in no clinically significant change compared with placebo (n = 23) in sex hormone-binding globulin, estradiol, luteinizing hormone, follicle-stimulating hormone, thyroxine (free T4), and dehydroepiandrosterone. Statistically significant, baseline-adjusted mean increases compared with placebo were observed for total testosterone at 8 weeks (97.1 ng/dL, $P<0.003$) and thyroid-stimulating hormone at 52 weeks (0.4 mcIU/mL, $P<0.05$). The median percentage changes from baseline within the dutasteride group were 17.9% for testosterone at 8 weeks and 12.4% for thyroid-stimulating hormone at 52 weeks. After stopping dutasteride for 24 weeks, the mean levels of testosterone and thyroid-stimulating hormone had returned to baseline in the group of subjects with available data at the visit. In patients with BPH treated with dutasteride in a large randomized, double-blind, placebo-controlled study, there was a median percent increase in luteinizing hormone of 12% at 6 months and 19% at both 12 and 24 months.

Other Effects: Plasma lipid panel and bone mineral density were evaluated following 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone mineral density as measured by dual energy x-ray absorptiometry compared with either placebo or baseline. In addition, the plasma lipid profile (i.e., total cholesterol, low density lipoproteins, high density lipoproteins, and triglycerides) was unaffected by dutasteride. No clinically significant changes in adrenal hormone responses to ACTH stimulation were observed in a subset population (n = 13) of the 1-year healthy volunteer study.

12.3 Pharmacokinetics

Absorption: Following administration of a single 0.5-mg dose of a soft gelatin capsule, time to peak serum concentrations (T_{max}) of dutasteride occurs within 2 to 3 hours. Absolute bioavailability in 5 healthy subjects is approximately 60% (range, 40% to 94%). When the drug

is administered with food, the maximum serum concentrations were reduced by 10% to 15%. This reduction is of no clinical significance.

Distribution: Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6%).

In a study of healthy subjects (n = 26) receiving dutasteride 0.5 mg/day for 12 months, semen dutasteride concentrations averaged 3.4 ng/mL (range, 0.4 to 14 ng/mL) at 12 months and, similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months 11.5% of serum dutasteride concentrations partitioned into semen.

Metabolism and Elimination: Dutasteride is extensively metabolized in humans. In vitro studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes. Both of these isoenzymes produced the 4′-hydroxydutasteride, 6-hydroxydutasteride, and the 6,4′-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was formed by CYP3A4. Dutasteride is not metabolized in vitro by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. In human serum following dosing to steady state, unchanged dutasteride, 3 major metabolites (4′-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride), and 2 minor metabolites (6,4′-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl additions in the 6 and 15 positions is not known. In vitro, the 4′-hydroxydutasteride and 1,2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of human 5α-reductase. The activity of 6β-hydroxydutasteride is comparable to that of dutasteride.

Dutasteride and its metabolites were excreted mainly in feces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range, 5% to 97%).

The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state. The average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

Specific Populations: *Pediatric:* Dutasteride pharmacokinetics have not been investigated in subjects younger than 18 years.

Geriatric: No dose adjustment is necessary in the elderly. The pharmacokinetics and pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects aged between 24 and 87 years following administration of a single 5-mg dose of dutasteride. In this single-dose study, dutasteride half-life increased with age (approximately 170 hours in men aged 20 to 49 years, approximately 260 hours in men aged 50 to 69 years, and approximately 300 hours in men older than 70 years). Of 2,167 men treated with dutasteride in the 3 pivotal studies, 60%

were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

Gender: AVODART is contraindicated in pregnancy and women of childbearing potential and is not indicated for use in other women *[see Contraindications (4), Warnings and Precautions (5.1)]*. The pharmacokinetics of dutasteride in women have not been studied.

Race: The effect of race on dutasteride pharmacokinetics has not been studied.

Renal Impairment: The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5-mg dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic Impairment: The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients.

Drug Interactions: No clinical drug interaction studies have been performed to evaluate the impact of CYP3A enzyme inhibitors on dutasteride pharmacokinetics. However, based on in vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4/5 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, troleandomycin, and ciprofloxacin.

Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1,000 ng/mL, 25 times greater than steady-state serum concentrations in humans.

Alpha-Adrenergic Blocking Agents: In a single-sequence, crossover study in healthy volunteers, the administration of tamsulosin or terazosin in combination with AVODART had no effect on the steady-state pharmacokinetics of either alpha-adrenergic blocker. Although the effect of administration of tamsulosin or terazosin on dutasteride pharmacokinetic parameters was not evaluated, the percent change in DHT concentrations was similar for AVODART alone compared with the combination treatment.

Calcium Channel Antagonists: In a population pharmacokinetics analysis, a decrease in clearance of dutasteride was noted when coadministered with the CYP3A4 inhibitors verapamil (-37%, n = 6) and diltiazem (-44%, n = 5). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist that is not a CYP3A4 inhibitor, was coadministered with dutasteride (+7%, n = 4).

The decrease in clearance and subsequent increase in exposure to dutasteride in the presence of verapamil and diltiazem is not considered to be clinically significant. No dose adjustment is recommended.

Cholestyramine: Administration of a single 5-mg dose of AVODART followed 1 hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in 12 normal volunteers.

Digoxin: In a study of 20 healthy volunteers, AVODART did not alter the steady-state

pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

Warfarin: In a study of 23 healthy volunteers, 3 weeks of treatment with AVODART 0.5 mg/day did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of warfarin on prothrombin time when administered with warfarin.

Other Concomitant Therapy: Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in the 3 Phase 3 pivotal efficacy studies receiving AVODART were taking other medications concomitantly. No clinically significant adverse interactions could be attributed to the combination of AVODART and concurrent therapy when AVODART was coadministered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: A 2-year carcinogenicity study was conducted in B6C3F1 mice at doses of 3, 35, 250, and 500 mg/kg/day for males and 3, 35, and 250 mg/kg/day for females; an increased incidence of benign hepatocellular adenomas was noted at 250 mg/kg/day (290-fold the expected clinical exposure to a 0.5-mg daily dose) in females only. Two of the 3 major human metabolites have been detected in mice. The exposure to these metabolites in mice is either lower than in humans or is not known.

In a 2-year carcinogenicity study in Han Wistar rats, at doses of 1.5, 7.5, and 53 mg/kg/day for males and 0.8, 6.3, and 15 mg/kg/day for females, there was an increase in Leydig cell adenomas in the testes at 53 mg/kg/day (135-fold the expected clinical exposure). An increased incidence of Leydig cell hyperplasia was present at 7.5 mg/kg/day (52-fold the expected clinical exposure) and 53 mg/kg/day in male rats. A positive correlation between proliferative changes in the Leydig cells and an increase in circulating luteinizing hormone levels has been demonstrated with 5α-reductase inhibitors and is consistent with an effect on the hypothalamic-pituitary-testicular axis following 5α-reductase inhibition. At tumorigenic doses in rats, luteinizing hormone levels in rats were increased by 167%. In this study, the major human metabolites were tested for carcinogenicity at approximately 1 to 3 times the expected clinical exposure.

Mutagenesis: Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats. The results did not indicate any genotoxic potential of the parent drug. Two major human metabolites were also negative in either the Ames test or an abbreviated Ames test.

Impairment of Fertility: Treatment of sexually mature male rats with dutasteride at doses of 0.05, 10, 50, and 500 mg/kg/day (0.1- to 110-fold the expected clinical exposure of parent drug) for up to 31 weeks resulted in dose- and time-dependent decreases in fertility; reduced

cauda epididymal (absolute) sperm counts but not sperm concentration (at 50 and 500 mg/kg/day); reduced weights of the epididymis, prostate, and seminal vesicles; and microscopic changes in the male reproductive organs. The fertility effects were reversed by recovery week 6 at all doses, and sperm counts were normal at the end of a 14-week recovery period. The 5α-reductase–related changes consisted of cytoplasmic vacuolation of tubular epithelium in the epididymides and decreased cytoplasmic content of epithelium, consistent with decreased secretory activity in the prostate and seminal vesicles. The microscopic changes were no longer present at recovery week 14 in the low-dose group and were partly recovered in the remaining treatment groups. Low levels of dutasteride (0.6 to 17 ng/mL) were detected in the serum of untreated female rats mated to males dosed at 10, 50, or 500 mg/kg/day for 29 to 30 weeks.

In a fertility study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in reduced litter size, increased embryo resorption and feminization of male fetuses (decreased anogenital distance) at doses of ≥2.5 mg/kg/day (2- to 10-fold the clinical exposure of parent drug in men). Fetal body weights were also reduced at ≥0.05 mg/kg/day in rats (<0.02-fold the human exposure).

13.2 Animal Toxicology

Central Nervous System Toxicology Studies: In rats and dogs, repeated oral administration of dutasteride resulted in some animals showing signs of non-specific, reversible, centrally-mediated toxicity without associated histopathological changes at exposure 425- and 315-fold the expected clinical exposure (of parent drug), respectively.

13.3 Reproductive and Developmental Toxicity

In an intravenous embryo-fetal development study in the rhesus monkey (12/group), administration of dutasteride at 400, 780, 1,325, or 2,010 ng/day on gestation days 20 to 100 did not adversely affect development of male external genitalia. Reduction of fetal adrenal weights, reduction in fetal prostate weights, and increases in fetal ovarian and testis weights were observed in monkeys treated with the highest dose. Based on the highest measured semen concentration of dutasteride in treated men (14 ng/mL), these doses represent 0.8 to 16 times based on blood levels of parent drug (32 to 186 times based on a ng/kg daily dose) the potential maximum exposure of a 50-kg human female to 5 mL semen daily from a dutasteride-treated man, assuming 100% absorption. Dutasteride is highly bound to proteins in human semen (>96%), potentially reducing the amount of dutasteride available for vaginal absorption.

In an embryo-fetal development study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in feminization of male fetuses (decreased anogenital distance) and male offspring (nipple development, hypospadias, and distended preputial glands) at all doses (0.07- to 111-fold the expected male clinical exposure). An increase in stillborn pups was observed at 30 mg/kg/day, and reduced fetal body weight was observed at doses ≥2.5 mg/kg/day (15- to 111-fold the expected clinical exposure). Increased incidences of skeletal variations considered to be delays in ossification associated with reduced body weight were observed at doses of 12.5 and 30 mg/kg/day (56- to 111-fold the expected clinical

exposure).

In an oral pre- and post-natal development study in rats, dutasteride doses of 0.05, 2.5, 12.5, or 30 mg/kg/day were administered. Unequivocal evidence of feminization of the genitalia (i.e., decreased anogenital distance, increased incidence of hypospadias, nipple development) of F1 generation male offspring occurred at doses ≥2.5 mg/kg/day (14- to 90-fold the expected clinical exposure in men). At a daily dose of 0.05 mg/kg/day (0.05-fold the expected clinical exposure), evidence of feminization was limited to a small, but statistically significant, decrease in anogenital distance. Doses of 2.5 to 30 mg/kg/day resulted in prolonged gestation in the parental females and a decrease in time to vaginal patency for female offspring and a decrease in prostate and seminal vesicle weights in male offspring. Effects on newborn startle response were noted at doses greater than or equal to 12.5 mg/kg/day. Increased stillbirths were noted at 30 mg/kg/day.

In the rabbit, embryo-fetal study doses of 30, 100, and 200 mg/kg (28- to 93-fold the expected clinical exposure in men) were administered orally on days 7 to 29 of pregnancy to encompass the late period of external genitalia development. Histological evaluation of the genital papilla of fetuses revealed evidence of feminization of the male fetus at all doses. A second embryo-fetal study in rabbits at doses of 0.05, 0.4, 3.0, and 30 mg/kg/day (0.3- to 53-fold the expected clinical exposure) also produced evidence of feminization of the genitalia in male fetuses at all doses. It is not known whether rabbits or rhesus monkeys produce any of the major human metabolites.

14 CLINICAL STUDIES

14.1 Monotherapy

AVODART 0.5 mg/day (n = 2,167) or placebo (n = 2,158) was evaluated in male subjects with BPH in three 2-year multicenter, placebo-controlled, double-blind studies, each with 2-year open-label extensions (n = 2,340). More than 90% of the study population was Caucasian. Subjects were at least 50 years of age with a serum PSA ≥1.5 ng/mL and <10 ng/mL and BPH diagnosed by medical history and physical examination, including enlarged prostate (≥30 cc) and BPH symptoms that were moderate to severe according to the American Urological Association Symptom Index (AUA-SI). Most of the 4,325 subjects randomly assigned to receive either dutasteride or placebo completed 2 years of double-blind treatment (70% and 67%, respectively). Most of the 2,340 subjects in the study extensions completed 2 additional years of open-label treatment (71%).

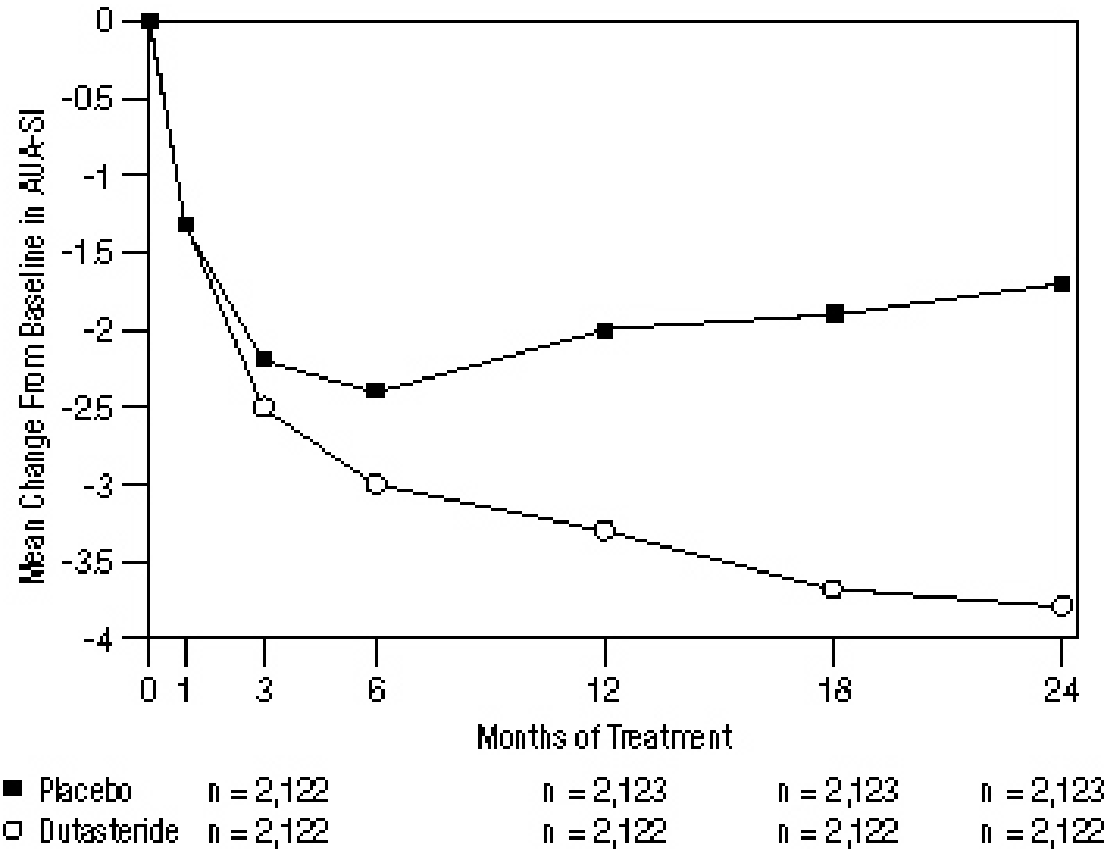
Effect on Symptom Scores: Symptoms were quantified using the AUA-SI, a questionnaire that evaluates urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) by rating on a 0 to 5 scale for a total possible score of 35. The baseline AUA-SI score across the 3 studies was approximately 17 units in both treatment groups.

Subjects receiving dutasteride achieved statistically significant improvement in symptoms versus placebo by Month 3 in 1 study and by Month 12 in the other 2 pivotal studies.

At Month 12, the mean decrease from baseline in AUA-SI symptom scores across the 3 studies pooled was -3.3 units for dutasteride and -2.0 units for placebo with a mean difference between the 2 treatment groups of -1.3 (range, -1.1 to -1.5 units in each of the 3 studies, $P<0.001$) and was consistent across the 3 studies. At Month 24, the mean decrease from baseline was -3.8 units for dutasteride and -1.7 units for placebo with a mean difference of -2.1 (range, -1.9 to -2.2 units in each of the 3 studies, $P<0.001$). See Figure 1. The improvement in BPH symptoms seen during the first 2 years of double-blind treatment was maintained throughout an additional 2 years of open-label extension studies.

These studies were prospectively designed to evaluate effects on symptoms based on prostate size at baseline. In men with prostate volumes ≥40 cc, the mean decrease was -3.8 units for dutasteride and -1.6 units for placebo, with a mean difference between the 2 treatment groups of -2.2 at Month 24. In men with prostate volumes <40 cc, the mean decrease was -3.7 units for dutasteride and -2.2 units for placebo, with a mean difference between the 2 treatment groups of -1.5 at Month 24.

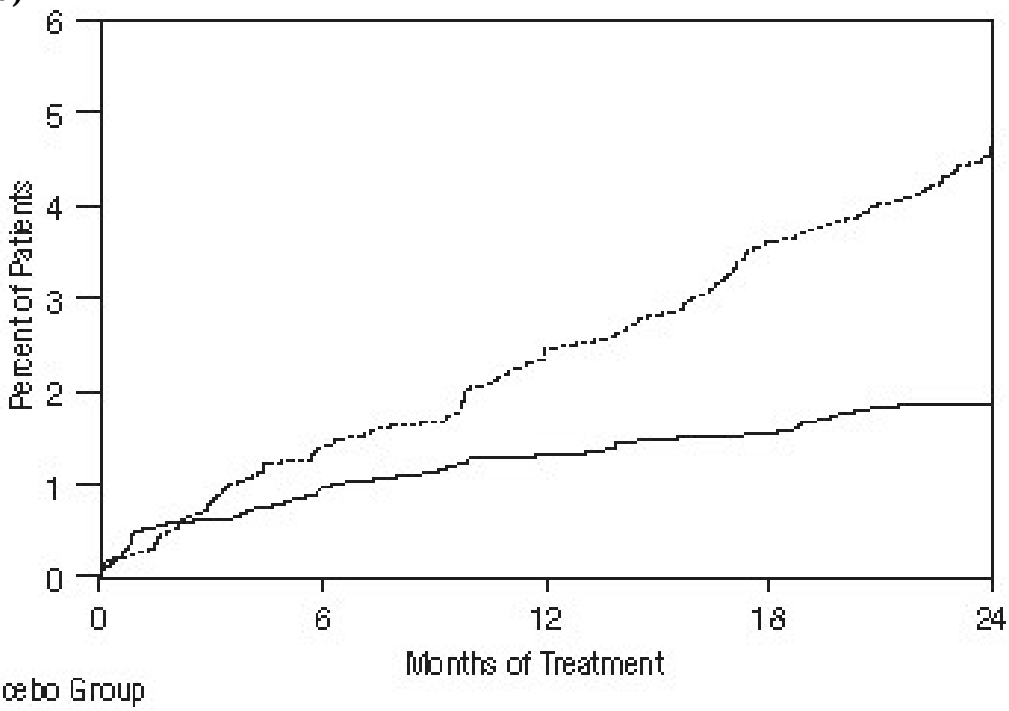
Figure 1. AUA-SI Score[a] Change from Baseline (Randomized, Double-Blind, Placebo-Controlled Studies Pooled)



[a] AUA-SI score ranges from 0 to 35.

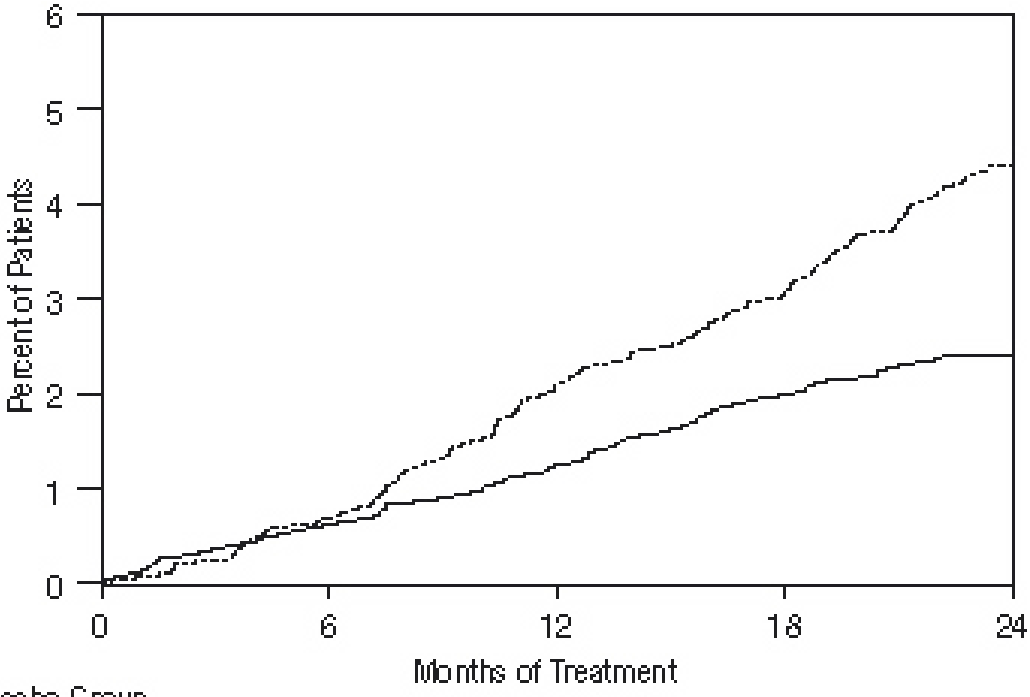
Effect on Acute Urinary Retention and the Need for Surgery: Efficacy was also assessed after 2 years of treatment by the incidence of AUR requiring catheterization and BPH-related urological surgical intervention. Compared with placebo, AVODART was associated with a statistically significantly lower incidence of AUR (1.8% for AVODART vs. 4.2% for placebo, *P*<0.001; 57% reduction in risk, [95% CI: 38% to 71%]) and with a statistically significantly lower incidence of surgery (2.2% for AVODART vs. 4.1% for placebo, *P*<0.001; 48% reduction in risk, [95% CI: 26% to 63%]). See Figures 2 and 3.

Figure 2. Percent of Subjects Developing Acute Urinary Retention Over a 24-Month Period (Randomized, Double-Blind, Placebo-Controlled Studies Pooled)



---- Placebo Group				
No. of events, cumulative	28	49	70	90
No. at risk	2,158	2,039	1,919	1,793
— Dutasteride Group				
No. of events, cumulative	19	27	31	39
No. at risk	2,167	2,052	1,928	1,827

Figure 3. Percent of Subjects Having Surgery for Benign Prostatic Hyperplasia Over a 24-Month Period (Randomized, Double-Blind, Placebo-Controlled Studies Pooled)



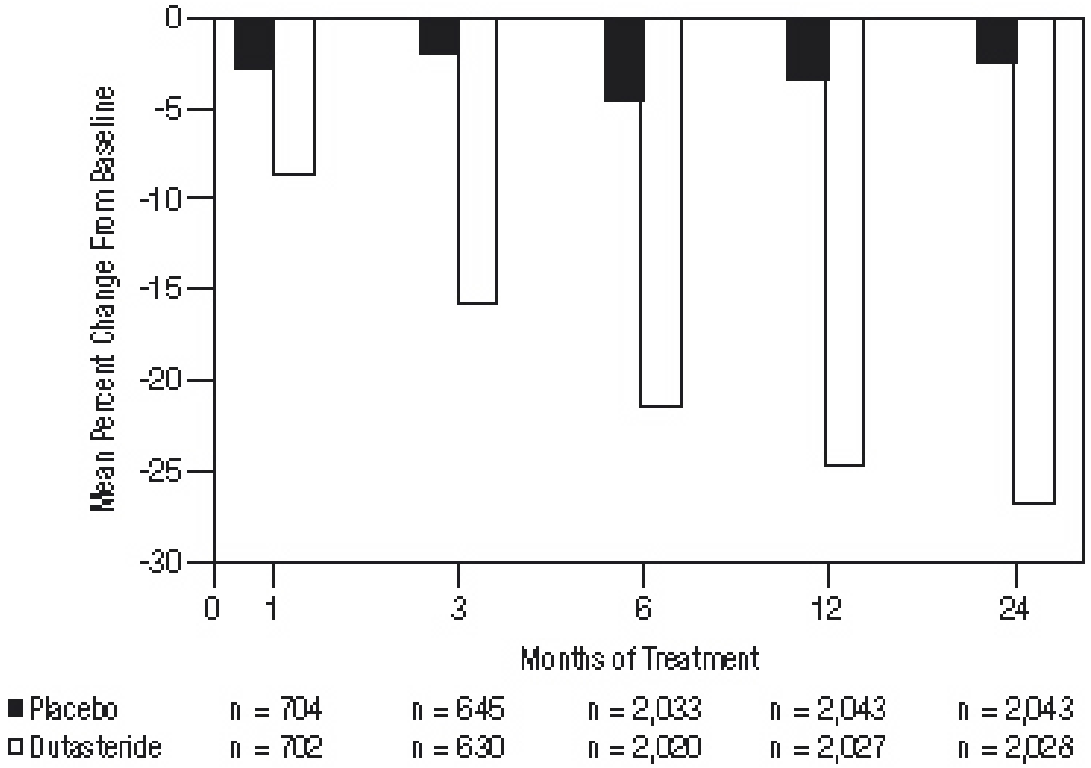
---- Placebo Group				
No. of events, cumulative	13	40	59	89
No. at risk	2,158	2,057	1,944	1,823
— Dutasteride Group				
No. of events, cumulative	12	25	39	47
No. at risk	2,167	2,064	1,944	1,846

Effect on Prostate Volume: A prostate volume of at least 30 cc measured by transrectal ultrasound was required for study entry. The mean prostate volume at study entry was approximately 54 cc.

Statistically significant differences (AVODART versus placebo) were noted at the earliest post-treatment prostate volume measurement in each study (Month 1, Month 3, or Month 6) and continued through Month 24. At Month 12, the mean percent change in prostate volume across the 3 studies pooled was -24.7% for dutasteride and -3.4% for placebo; the mean difference (dutasteride minus placebo) was -21.3% (range, -21.0% to -21.6% in each of the 3 studies, $P<0.001$). At Month 24, the mean percent change in prostate volume across the 3 studies pooled was -26.7% for dutasteride and -2.2% for placebo with a mean difference of -24.5% (range, -24.0% to -25.1% in each of the 3 studies, $P<0.001$). See Figure 4. The reduction in prostate volume seen during the first 2 years of double-blind treatment was maintained

throughout an additional 2 years of open-label extension studies.

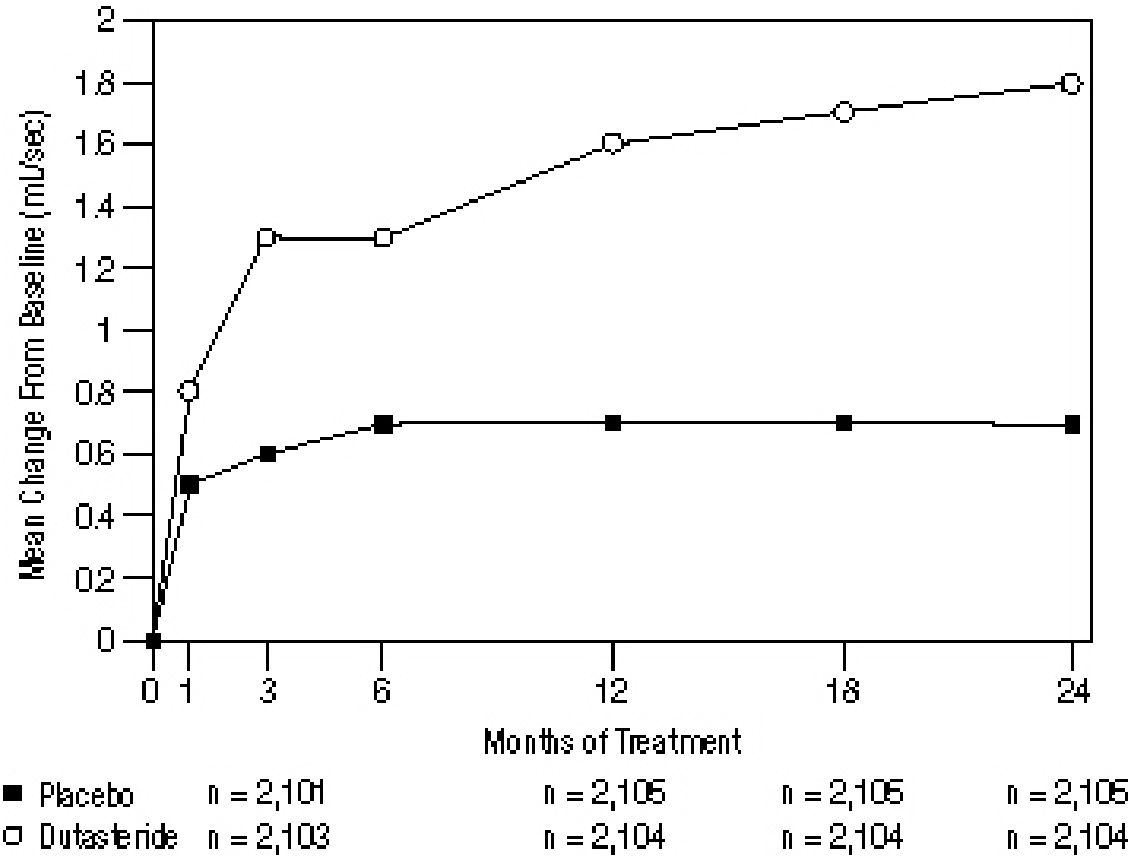
Figure 4. Prostate Volume Percent Change from Baseline (Randomized, Double-Blind, Placebo-Controlled Studies Pooled)



Effect on Maximum Urine Flow Rate: A mean peak urine flow rate (Q_{max}) of ≤15 mL/sec was required for study entry. Q_{max} was approximately 10 mL/sec at baseline across the 3 pivotal studies.

Differences between the 2 groups were statistically significant from baseline at Month 3 in all 3 studies and were maintained through Month 12. At Month 12, the mean increase in Q_{max} across the 3 studies pooled was 1.6 mL/sec for AVODART and 0.7 mL/sec for placebo; the mean difference (dutasteride minus placebo) was 0.8 mL/sec (range, 0.7 to 1.0 mL/sec in each of the 3 studies, $P<0.001$). At Month 24, the mean increase in Q_{max} was 1.8 mL/sec for dutasteride and 0.7 mL/sec for placebo, with a mean difference of 1.1 mL/sec (range, 1.0 to 1.2 mL/sec in each of the 3 studies, $P<0.001$). See Figure 5. The increase in maximum urine flow rate seen during the first 2 years of double-blind treatment was maintained throughout an additional 2 years of open-label extension studies.

Figure 5. Q_{max} Change from Baseline (Randomized, Double-Blind, Placebo-Controlled Studies Pooled)



Summary of Clinical Studies: Data from 3 large, well-controlled efficacy studies demonstrate that treatment with AVODART (0.5 mg once daily) reduces the risk of both AUR and BPH-related surgical intervention relative to placebo, improves BPH-related symptoms, decreases prostate volume, and increases maximum urinary flow rates. These data suggest that AVODART arrests the disease process of BPH in men with an enlarged prostate.

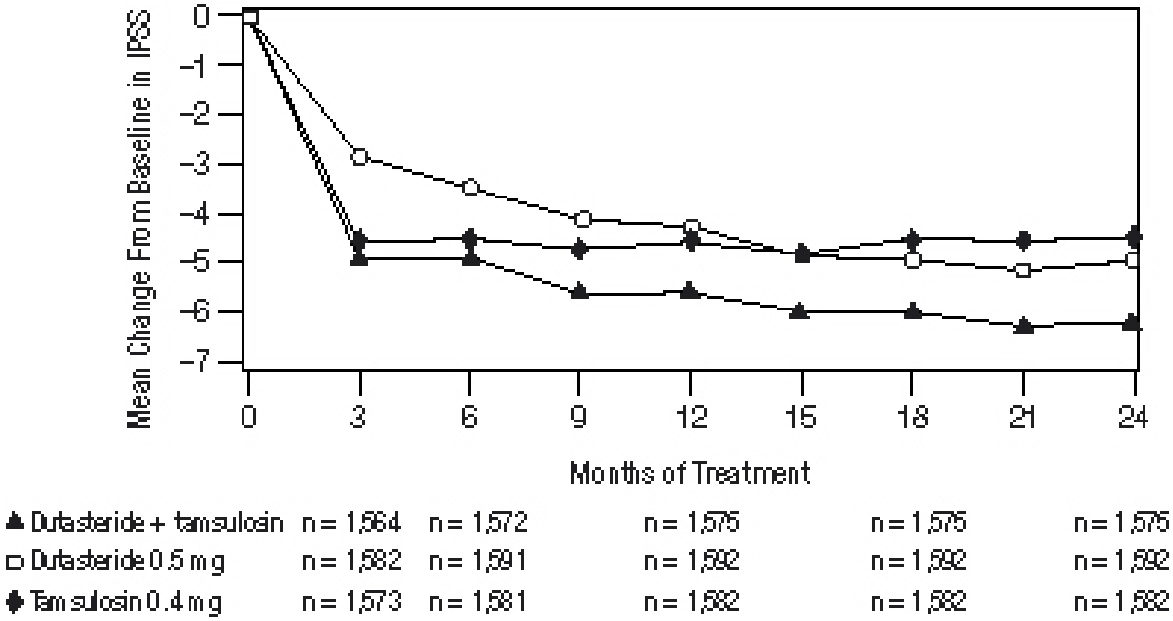
14.2 Combination With Alpha-Blocker Therapy (CombAT)

The efficacy of combination therapy (AVODART 0.5 mg/day plus tamsulosin 0.4 mg/day, n = 1,610) was compared with AVODART alone (n = 1,623) or tamsulosin alone (n = 1,611) in a 4-year multicenter, randomized, double-blind study. Study entry criteria were similar to the Phase 3 monotherapy efficacy trials described above in section 14.1. The results presented below are from data collected following 2 years of treatment in the 4-year study. Eighty-eight percent (88%) of the enrolled study population was Caucasian. Approximately 52% of subjects had previous exposure to 5α-reductase inhibitor or alpha-blocker treatment. The primary efficacy endpoint evaluated during the first 2 years of treatment was change in international prostate symptom score (IPSS). Most of the 4,844 subjects randomly assigned to receive combination, AVODART, or tamsulosin completed 2 years of double-blind treatment

(79%, 80%, and 78%, respectively).

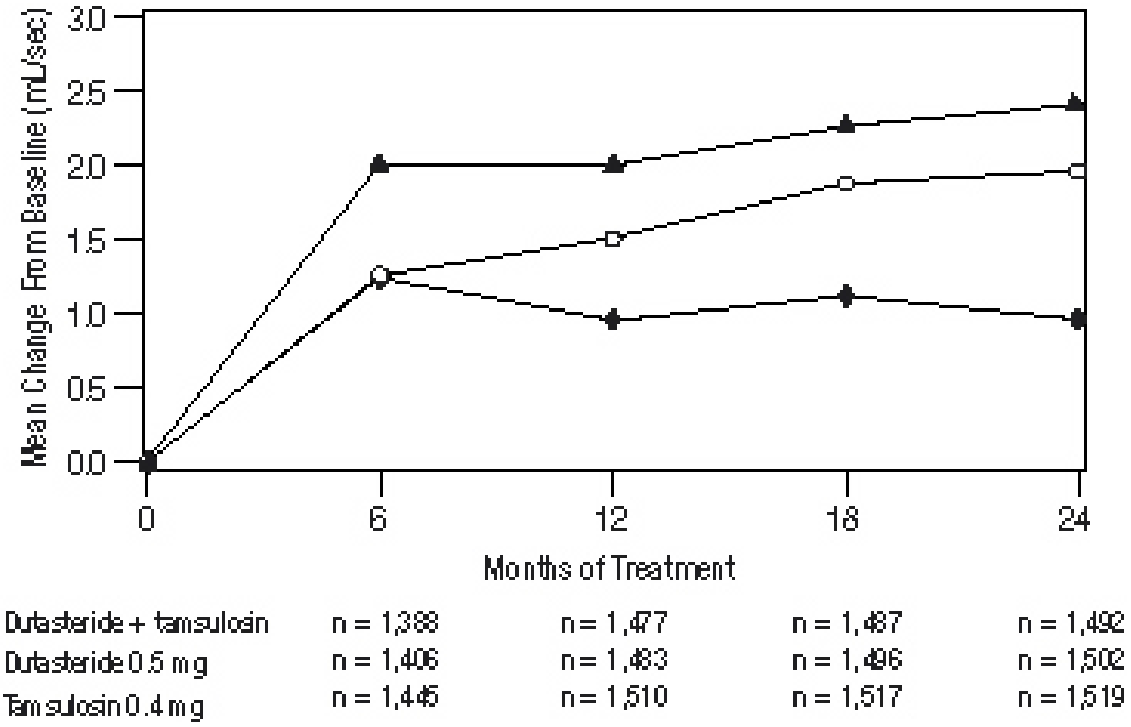
Effect on Symptom Score: Symptoms were quantified using the first 7 questions of the IPSS (identical to the AUA-SI). The baseline score was approximately 16.4 units for each treatment group. Combination therapy was statistically superior to each of the monotherapy treatments in decreasing symptom score at Month 24. This difference was seen by Month 9 and continued through Month 24. At Month 24, the mean change from baseline (±SD) in IPSS symptom scores was -6.2 (±7.14) for combination, -4.9 (±6.81) for AVODART, and -4.3 (±7.01) for tamsulosin, with a mean difference between combination and AVODART of -1.3 units (P<0.001; [95% CI: -1.69, -0.86]), and between combination and tamsulosin of -1.8 units (P<0.001; [95% CI: -2.23, -1.40]). See Figure 6.

Figure 6. International Prostate Symptom Score Change from Baseline (CombAT study)



Effect on Maximum Urine Flow Rate: The baseline Q_{max} was approximately 10.7 mL/sec for each treatment group. Combination therapy was statistically superior to each of the monotherapy treatments in increasing Q_{max} at Month 24. This difference was seen by Month 6 and continued through Month 24. At Month 24, the mean increase from baseline (±SD) in Q_{max} was 2.4 (±5.26) mL/sec for combination, 1.9 (±5.10) mL/sec for AVODART, and 0.9 (±4.57) mL/sec for tamsulosin, with a mean difference between combination and AVODART of 0.5 mL/sec (P = 0.003; [95% CI: 0.17, 0.84]), and between combination and tamsulosin of 1.5 mL/sec (P<0.001; [95% CI: 1.19, 1.86]). See Figure 7.

Figure 7. Q_{max} Change from Baseline (CombAT study)



Effect on Prostate Volume: The mean prostate volume at study entry was approximately 55 cc. At Month 24, the mean percent change from baseline (±SD) in prostate volume was -26.9% (±22.57) for combination therapy, -28.0% (±24.88) for AVODART, and 0% (±31.14) for tamsulosin, with a mean difference between combination and AVODART of 1.1% (*P* = NS; [95% CI: -0.6, 2.8]), and between combination and tamsulosin of -26.9% (*P*<0.001; [95% CI: -28.9, -24.9]).

16 HOW SUPPLIED/STORAGE AND HANDLING

AVODART Soft Gelatin Capsules 0.5 mg are oblong, opaque, dull yellow, gelatin capsules imprinted with “GX CE2” with red edible ink on one side packaged in bottles of 30 (NDC 0173-0712-15) and 90 (NDC 0173-0712-04) with child-resistant closures.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dutasteride is absorbed through the skin. AVODART Capsules should not be handled by women who are pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male fetus *[see Warnings and Precautions (5.1)]*.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

17.1 Exposure of Women—Risk to Male Fetus

Physicians should inform patients that AVODART Capsules should not be handled by a woman who is pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male fetus. Dutasteride is absorbed through the skin and could result in unintended fetal exposure. If a pregnant woman or woman of childbearing potential comes in contact with leaking AVODART Capsules, the contact area should be washed immediately with soap and water *[see Warnings and Precautions (5.1), Specific Populations (8.1)]*.

17.2 Blood Donation

Physicians should inform men treated with AVODART that they should not donate blood until at least 6 months following their last dose to prevent pregnant women from receiving dutasteride through blood transfusion *[see Warnings and Precautions (5.4)]*. Serum levels of dutasteride are detectable for 4 to 6 months after treatment ends *[see Clinical Pharmacology (12.3)]*.

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GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured by Catalent Pharma Solutions, Beinheim, France for
GlaxoSmithKline, Research Triangle Park, NC 27709

June 2010
AVT:5PI

PHARMACIST—DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Patient Information

AVODART® (dutasteride) Soft Gelatin Capsules

AVODART is for use by men only.

Read this information carefully before you start taking AVODART. Read the information you get with AVODART each time you refill your prescription. There may be new information. This information does not take the place of

talking with your doctor.

What is AVODART?
AVODART is a medication for the treatment of symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

- Improve symptoms
- Reduce the risk of acute urinary retention (a complete blockage of urine flow)
- Reduce the risk of the need for BPH-related surgery

AVODART is not a treatment for prostate cancer. See the end of this leaflet for information about how AVODART works.

Who should NOT take AVODART?

- Women and children should not take AVODART. A woman who is pregnant or capable of becoming pregnant should not handle AVODART capsules. See **"What are the special warnings for women about AVODART?"**
- Do not take AVODART if you have had an allergic reaction to AVODART or any of its ingredients.

What are the special warnings for women about AVODART?

- Women should never take AVODART.
- Women who are pregnant or may become pregnant should not handle AVODART Capsules. If a woman who is pregnant with a male baby gets enough AVODART into her body after swallowing it or through her skin after handling it, the male baby may be born with abnormal sex organs.

What are the special precautions about AVODART?

- Men treated with AVODART should not donate blood until at least 6 months after their final dose to prevent giving AVODART to a pregnant female through a blood transfusion.
- Tell your doctor if you have liver problems. AVODART may not be right for you.

How should I take AVODART?

- Take 1 AVODART capsule once a day.
- Swallow the capsule whole because the contents of the capsule may irritate your lips, mouth, or throat.
- You can take AVODART with or without food.
- If you miss a dose, you may take it later that day. Do not make up the

missed dose by taking 2 doses the next day.
- You may find it helpful to take AVODART at the same time every day to help you remember to take your dose.

What are the possible side effects of AVODART?
Possible side effects are impotence (trouble getting or keeping an erection), a decrease in libido (sex drive), enlarged breasts, a decrease in the amount of semen released during sex, and allergic reactions such as rash, itching, hives, and swelling of the lips or face. These events occurred infrequently.

Talk to your doctor about these and other possible side effects. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AVODART?
AVODART is a soft gelatin capsule that may become soft and leak or may stick to other capsules if kept at high temperatures. Store AVODART capsules at room temperature of 77°F (25°C) or lower.

If your capsules are cracked or leaking, don't use them, and contact your pharmacist.

General information about AVODART.
- Do not use AVODART for a condition for which it was not prescribed.
- Do not share your AVODART.
- Ask your doctor about how often you should return for a visit to check your BPH.
- A blood test called PSA (prostate-specific antigen) is sometimes used to detect prostate cancer. AVODART will reduce the amount of PSA measured in your blood. Your doctor is aware of this effect and can still use PSA to detect prostate cancer in you. Increases in your PSA levels from their lowest point while on treatment with AVODART (even if the PSA values are in the normal range) should be evaluated by your physician.
- If you have questions about AVODART, ask your doctor or pharmacist. They can show you detailed information about AVODART that was written for healthcare professionals.

How does AVODART work?
Prostate growth is caused by a hormone in the blood called

dihydrotestosterone (DHT). AVODART lowers DHT production in the body, leading to shrinkage of the enlarged prostate in most men. Just as your prostate became large over a long period of time, reducing the size of your prostate and improving your symptoms will take time. While some men have fewer problems and symptoms after 3 months of treatment with AVODART, a treatment period of at least 6 months is usually necessary to see if AVODART will work for you. Studies have shown that treatment with AVODART for 2 years reduces the risk of complete blockage of urine flow (acute urinary retention) and/or the need for surgery for benign prostatic hyperplasia.

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